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# FIRST ANNUAL REPORT ON CARCINOGENS

## JULY 1980

**VOLUME 2**

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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

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# FIRST ANNUAL REPORT ON CARCINOGENS

Pursuant to Section 301(b) (4) of the
Public Health Service Act as Amended
by Section 262, PL 95-622

JULY 1980

## VOLUME II

Department of Health and Human Services

Prepared by
National Toxicology Program
U.S. Public Health Service

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READEX FICHE

# PART I

## Selected Data Taken from Those IARC Monographs Dealing with the 26 Chemicals or Industrial Processes Considered in This Report

## IARC REVIEWED SUBSTANCES

| Substances | IARC Vol., Page |
|---|---|
| 1. aflatoxins | 1,145 |
| 2. 4-aminobiphenyl | 1,74 |
| 3. arsenic compounds | 2,48 |
| 4. asbestos | 14,11 |
| 5. auramine | 1,69 |
| 6. benzene | 7,203 |
| 7. benzidine | 1,80 |
| 8. N,N-Bis(2-chloroethyl)-2-napthylamine | 4,119 |
| 9. Bis(chloromethyl)ether | 4,231 |
| 10. cadmium | 11,39 |
| 11. chloramphenicol | 10,85 |
| 12. chloromethyl methyl ether | 4,239 |
| 13. chromium | 2,100 |
| 14. cyclophosphamide | 9,135 |
| 15. diethylstilbestrol | 6,55 |
| 16. hematite | 1,29 |
| 17. isopropyl oils | 15,223 |
| 18. melphalan | 9,167 |
| 19. mustard gas | 9,181 |
| 20. 2-naphthylamine | 4,97 |
| 21. nickel | 11,75 |
| 22. oxymetholone | 13,131 |
| 23. phenacetin | 13,141 |
| 24. phenytoin | 13,201 |
| 25. soot, tars, and oils | 3,22 |
| 26. vinyl chloride | 7,291 |

L. Tomatis et al.
Cancer Research 38: 877,1978

# Aflatoxins*

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Aflatoxin $B_1$ - Chem. Abstr. No.: 1162658; Name: Cyclopenta/c/furo/3', 2':4,5/furo/2,3-h/1/benzopyran-1,11-dione,2,3,6aα,9aα-tetrahydro-4-methoxy-

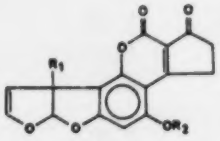
Aflatoxin $B_2$ - Chem. Abstr. No.: 7220817; Name: Cyclopenta/c/furo/3', 2':4,5/furo/2,3-h/1/benzopyran-1,11-dione,2,3,6aα,8,9,9aα-hexahydro-4-methoxy-

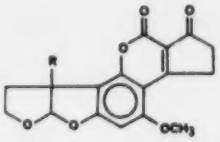
Aflatoxin $G_1$ - Chem. Abstr. No.: 1165395; Name: 1H,12H-Furo/3',2':4,5/furo/2,3-h/pyrano/3,4-c/1/benzopyran-1,12-dione,3,4,7a,10a-tetrahydro-5-methoxy-

Aflatoxin $G_2$ - Chem. Abstr. No.: 7241987; Name: 1H,12H-Furo/3',2':4,5/furo/2,3-h/pyrano/3,4-c/1/benzopyran-1,12-dione,3,4,7aα,9,10,10aα-hexahydro-5-methoxy-

Dihydroaflatoxin $G_1$

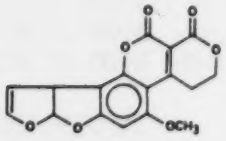
### 1.2 Chemical formula and molecular weight

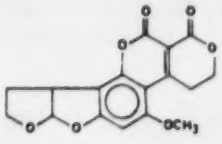




$B_1$: $R_1$=H; $R_2$=$CH_3$ Mol. wt: 312
$M_1$: $R_1$=OH; $R_2$=$CH_3$ Mol. wt: 328
$P_1$: $R_1$=H; $R_2$=H Mol. wt: 298

$B_2$: R=H Mol. wt: 314
$M_2$: R=OH Mol. wt: 330





$G_1$ Mol. wt: 328

$G_2$ Mol. wt: 330

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* Considered by the Working Group in Geneva, December 1971.

## 1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless to pale yellow crystals. Intensely fluorescent in ultraviolet light, emitting blue or yellow-green fluorescence, from which the designations "B" and "G" were derived.

(b) Melting-point; absorption spectroscopy: Data relating to these are given in the table below.

| Aflatoxin | Mol. formula | Mol. wt. | Melting point (°C) | Ultraviolet absorption maxima (nm) | ($\epsilon$x10$^{-4}$) | Fluorescence emission max. (nm) |
|---|---|---|---|---|---|---|
| $B_1$ | $C_{17}H_{12}O_6$ | 312 | 268-9 | 223<br>265<br>363 | 2.56<br>1.34<br>2.18 | 425 |
| $B_2$ | $C_{17}H_{14}O_6$ | 314 | 286-9 | 222<br>265<br>363 | 1.70<br>1.10<br>2.08 | 425 |
| $G_1$ | $C_{17}H_{12}O_7$ | 328 | 244-6 | 243<br>254<br>363 | 1.15<br>1.00<br>1.61 | 450 |
| $G_2$ | $C_{17}H_{14}O_7$ | 330 | 237-9 | 214<br>265<br>363 | 2.81<br>1.61<br>2.09 | 450 |
| $M_1$ | $C_{17}H_{12}O_7$ | 328 | 299 | 226<br>265<br>357 | 2.31<br>1.61<br>1.90 | 425 |
| $M_2$ | $C_{17}H_{14}O_7$ | 330 | 293 | 221<br>264<br>357 | 2.00<br>1.09<br>2.10 | 425 |
| $P_1$ | $C_{16}H_{10}O_6$ | 298 | - | 267<br>362 | -<br>- | - |

(c) Identity and purity test: Purity can conveniently be determined by visual examination under ultraviolet light of fluorescence on chromatograms. Picogram quantities can be discerned under optimum conditions.

(d) Solubility: Very slightly soluble in water (10-20 µg/ml) and insoluble in non-polar solvents. Freely soluble in moderately polar organic solvents (e.g., chloroform and methanol), and especially in dimethyl-sulfoxide.

(e) Stability: Relatively unstable to light and air, particularly in solutions in highly polar solvents. Fluorescent and non-fluorescent degradation products appear upon brief exposure of chromatograms to light. Chloroform solutions are stable for years if kept in the dark and cold.

(f) Chemical reactivity: The lactone ring is susceptible to alkaline hydrolysis. Aflatoxins in natural products are only partially destroyed under ordinary cooking conditions, but can be totally destroyed by drastic treatment such as autoclaving in the presence of ammonia or by treatment with hypochlorite.

## 2. Production, Use, Occurrence and Analysis

### 2.1 Use and Occurance

(a) Analytical methods

Chemical assay methods are available for the detection and quantification of aflatoxins in various foods and foodstuffs at concentrations of 1-5 ppb or higher (Pons, 1969). Bioassays, mainly for confirmation of chemical assay results, have also been devised (Legator, 1969).

Modifications of methods originally developed for peanuts have been devised for use on other commodities, such as cottonseed meal, corn, etc. Methodology for determining aflatoxin $M_1$ in milk is under development.

(b) Occurrence

Aflatoxin-producing fungal strains appear to be ubiquitously distributed. Therefore, virtually every foodstuff or food product is potentially susceptible to contamination under conditions (particularly of moisture and of temperature) favouring fungal

growth, which may occur at any stage of food production or subsequent processing. Some samples of nearly every major dietary staple have been found to contain some aflatoxin at one time or another. Adequate control measures, involving especially rapid post-harvest drying of crops and storage at moisture contents of less than 10 percent can virtually eliminate contamination.

Under inadequate conditions, contamination occurs in a given locality with great variability with regard to types of food affected, frequency of contamination and levels of aflatoxin present. However, the following generalizations are possible: (i) aflatoxin $B_1$ is most frequently present in contaminated samples; $B_2$ abd $G_1$ are present much less frequently and almost never in the absence of $B_1$; (ii) Dietary surveys in Uganda and in Thailand and Swaziland have revealed that peanuts, beans and corn were the principal vectors of aflatoxins, with many samples (up to 50 percent of market samples of peanuts) containing 0.1 ppm to 1 ppm aflatoxins; other grains such as rice were rarely contaminated (Alpert et al., 1971; Keen and Martin, 1971; Shank et al., 1972c).

In different regions of Murang'a (Kenya) mean aflatoxin levels of 0.121-0.351 µg per kg of food and of 0.05-0.167 µg per litre of beer have been detected (IARC, 1972).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Aflatoxins $B_1$ and $G_1$ are carcinogenic in four animal species, including tumours of the liver and some other organs following several routes of administration, including oral exposure. In the only feeding study in the mouse, this species appeared to be resistant to the carcinogenic effect observed in other species. No tumours have been observed in the monkey following several years of dosing: experiments are still in progress.

Aflatoxin $M_1$ produced liver tumours in the trout and aflatoxin $B_2$ in the rat, but only at doses more than 100 times higher than $B_1$.

## 4.2 Human data

Considerable evidence is now available to indicate that the market samples of some food commodities in some countries often contain aflatoxins. Increased frequency of liver cancer has been recorded in populations consuming diets contaminated by aflatoxins and possibly other mycotoxins, but no causal relationship has been established.

# 4-Aminobiphenyl

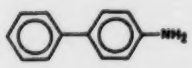
## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. No.: 92671; Name: 4-Biphenylamine

p-Aminobiphenyl; p-Aminodiphenyl; 4-Aminodiphenyl; p-Biphenylamine; p-Phenylaniline; Xenylamine

### 1.2 Chemical formula and molecular weight



$C_{12}H_{11}N$ Mol. wt: 169.22

### 1.3 Chemical and physical properties of the pure substance

(a) Description: A colourless, crystalline compound that darkens on oxidation

(b) Boiling-point: 191°C (15 mm)

(c) Melting-point: 53°C

(d) Solubility: Very slightly soluble in cold water; soluble in hot water and non-polar solvents; soluble in liquids.

(e) Chemical reactivity: A weak base that forms salts with HCl, $H_2SO_4$, etc.; can be diazotized to yield coloured coupling products; is oxidized by air and its amino group can be acetylated and alkylated

(f) Technical products and impurities: 2-Aminobiphenyl probably occurs as an impurity.

---

* Considered by the Working Group in Geneva, December 1971.

1 Data from Chemical Information Services, Stanford Research Institute

## 2. Production, Use, Occurrence and Analysis

### 2.1 Use and Occurrence

(a) Use

At least in one country 4-aminobiphenyl was manufactured from 1935 to 1955 (Melick et al., 1955) and used as a highly efficient rubber antioxidant, but recent information suggests that it is no longer commercially produced.[1]

(b) Analytical methods

Guidelines for the analysis of aromatic amines have been given (UICC, 1970).

(c) Occurrence

It was alleged to occur as an impurity in pre-1900 samples of aniline (Walpole et al., 1952) and is present in some samples of diphenylamine.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

4-Aminobiphenyl is carcinogenic in the mouse, rat, rabbit and dog. Following its oral administration it has produced bladder and liver tumours in mice and bladder papillomas and carcinomas in rabbits and dogs.

### 4.2 Human data

In the epidemiological studies, confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, a high incidence of bladder carcinomas was reported. In consequence one can say that bladder cancer was strongly associated with occupational exposure to 4-aminobiphenyl.

## Arsenic and Inorganic Arsenic Compounds

### 1. Chemical and Physical Data

#### 1.1 Identity

| Chemical Name | Formula | Chemical Abstract No. | Synonyms |
|---|---|---|---|
| Arsenic[1] | As | 7440-38-2 | None found |
| Arsenic trioxide[1,2] | $As_2O_3$ | 1327-53-3 | Arsenic (III) oxide<br>Arsenic sesquioxide<br>Arsenious acid<br>Arsenious oxide<br>Arsenious trioxide<br>Arsenite<br>Arsenolite<br>Arsenous acid<br>Arsenous acid anhydride<br>Arsenous oxide<br>Arsenous oxide anhydride<br>Claudelite<br>Crude arsenic<br>White arsenic |
| Arsenic pentoxide[2] | $As_2O_5$ | 1303-28-2 | Arsenic acid anhydride<br>Arsenic oxide<br>Arsenic (V) oxide |
| Calcium arsenate | $Ca_3(AsO_4)_2$ | 10103-62-5 | Calcium orthoarsenate<br>Tricalcium arsenate |
| Calcium arsenite | $CaAsO_3H$ | 27152-57-4 | Calcium meta-arsenite<br>Monocalcium arsenite |
| Potassium arsenate[3] | $KH_2AsO_4$ | 7784-41-0 | Arsenic acid, monopotassium salt<br>Macquer's salt<br>Potassium acid arsenate |

* Considered by the Working Group in Lyon, December 1972

| Chemical Name | Formula | Chemical Abstract No. | Synonyms |
|---|---|---|---|
| | | | Potassium arsenate, mono-basic<br>Potassium dihydrogen arsenate |
| Potassium arsenite | $KH(AsO_2)_2.H_2O$[4] | 13464-35-2 | Arsenious acid, potassium salt<br>Fowler's solution<br>Potassium meta-arsenite |
| Sodium arsenate | $Na_3AsO_4.12H_2O$[5] | 7631-89-2 | Sodium ortho-arsenate<br>Arsenic acid, sodium salt |
| Disodium hydrogen arsenate | $Na_2HAsO_4.7H_2O$[5] | 10048-95-0 | Arsenic acid, disodium salt hepta-hydrate<br>Disodium arsenate<br>Sodium acid arsenate<br>Sodium arsenate, dibasic |
| Sodium arsenate | $NaAsO_2$[4] | 7784-46-5 | Arsenious acid sodium salt<br>Sodium meta-arsenite |

Footnotes to table:

1 $As_2O_3$ is sometimes erroneously called "arsenic"

2 $As_2O_3$ is sometimes called "arsenic oxide", but this name is more properly used for $As_2O_5$. It is relatively common practice for the term arsenic acid to be used for $As_2O_5$ as well as for the various hydrated products ($H_3AsO_4$, $H_3AsO_3$, $H_4As_2O_7$).

3 The other salts, $K_3AsO_4$ and $K_2HAsO_4$, do not appear to be commercial products.

4 The commercial material has a somewhat variable composition.

5 The name "sodium arsenate" is applied to both the disodium and the trisodium salts. Because of this confusing use of terms, it is not always possible to determine which substance is under discussion.

## 1.2 Solubility

The compounds of arsenic considered in this monograph are all soluble in water, although arsenic itself is insoluble. The trioxide and the two calcium salts are of limited solubility. The sodium salts as well as the trioxide are also somewhat soluble in alcohols.

## 1.3 Stability

The arsenic compounds considered are in many cases not stable and well-defined materials. For example, the arsenites of alkali metals are slowly converted in solution to arsenates by atmospheric oxygen. These same materials in their dry state are said to be decomposed by atmospheric $CO_2$.

It is strongly recommended that investigators working with these compounds exercise great care to ensure that the material studied is in fact the one reported.

## 2. Production, Use, Occurrence and Analysis

### (a) Use

Arsenic: Arsenic is produced commercially by reduction of arsenic trioxide with charcoal. Almost all of the 1.07 million pounds of arsenic metal consumed in the United States in 1971 was imported from Sweden, the world's largest producer of arsenic trioxide. An approximate consumption pattern (expressed in million pounds) for the United States in 1971 is as follows: alloying additive, 0.96; electronic devices, 0.08; veterinary medicines, 0.03; total, 1.07 million pounds.

Arsenic pentoxide: Arsenic pentoxide is manufactured commercially by the oxidation of arsenic trioxide with nitric acid followed by the dehydration of the intermediate crystalline orthoarsenic acid hydrate. It seems likely that total annual US production (exclusive of material used as a non-isolated intermediate) does not exceed 1.25-1.5 million pounds.

It is believed that virtually all of the arsenic pentoxide or arsenic acid that is not used as an intermediate for production of metal arsenates is used as a pre-harvest defoliant (desiccant) for cotton and as an ingredient in formulated wood preservatives, known as Boliden salts.

Arsenic trioxide: Arsenic trioxide is produced commercially as a byproduct of metal refining operations. It is present in flue dusts from the roasting of ores, particularly those produced in copper refining. The condensate from this flue dust is termed "crude arsenic" (90-95 percent arsenic trioxide). Resubliming produces "white arsenic" (99 percent arsenic trioxide).

US production of arsenic trioxide in 1968 has been estimated at 7.7 million pounds from domestic ores and 8.5 million pounds from imported ores. Imports were 50.4 million pounds in 1968, but dropped to 32.8 million pounds in 1971.

Major producing countries for arsenic trioxide are Sweden, France, USSR, Mexico and South-West Africa. The consumption pattern for arsenic trioxide in the US in 1968 is believed to have been as follows: pesticides, 77 percent of total; glass, 18 percent; industrial inorganic chemicals, 4 percent; medicine, 1 percent.

Arsenic trioxide compositions are used as such as an insecticide for dormant application on grapes, in insecticidal dips for goats and sheep, and in combination with mercuric chloride in fungicides for treating fenceposts. By far its biggest use in the pesticide is in the synthesis of other arsenic-containing pesticides, such as lead, calcium and sodium arsenates, sodium arsenite and arsenic pentoxide.

Arsenic trioxide is widely used as a decolouring additive in the manufacture of nearly all colourless glass, in many coloured glasses, and in certain enamels. Among its uses in the production of industrial inorganic chemicals are purification of synthesis gas and the manufacture of pigments.

Consumption of arsenic trioxide in medicine is believed to be largely by way of arsenic trioxide-based organic arsenicals, although in the past arsenic trioxide itself reportedly has been used in human and veterinary medicine.

Calcium arsenate: Calcium arsenate is probably produced commercially by the reaction of calcium hydroxide with arsenic pentoxide or arsenic acid.

Production of commercial calcium arsenate [70 percent $Ca_3(AsO_4)_2$] in the US has declined rapidly from a level of 84 million pounds in 1942 to only 0.94 million pounds in 1971.

Historically, calcium arsenate was used mainly as an insecticide, with lesser quantities being used as a herbicide. Although there have been large variations in total consumption from year to year (depending on the extent of the cotton boll-weevil problem), consumption has shown a dramatic downward trend from the high levels of the 1940s. Government restriction on its use as an insecticide have been a factor in this fall. Consumption had been mainly in boll-weevil control, and also for the control of leaf-eating insects on tobacco and a variety of fruits and vegetables.

The remaining major applications, as of mid-1971, are believed to have been as a herbicide for turf, as a larvicide on poultry droppings for fly control, and on tomatoes for control of hornworms and fruit worms.

Calcium arsenite: Calcium arsenite is reportedly produced by the reaction of calcium chloride with arsenic trioxide. The amount made in the US is believed to be quite small.

Although calcium arsenite is reported to be useful as a germicide and as an insecticide, it apparently is not registered with US Federal agencies for use in these applications. No evidence was found of any present commercial usage.

Lead arsenate: Commercial lead arsenate products are believed to be produced by the reaction of arsenic pentoxide with lead oxide.

Combined production of acid and basic lead arsenate in the US declined rapidly from a level of 90.7 million pounds in 1944 to only 4.16 million pounds in 1970 and increased to 6.17 million pounds in 1971.

It is believed that the major use of lead arsenate occurred first in 1892 as an insecticide against the gypsy moth. It was used against the codling moth (e.g., in apple orchards) and other chewing insects (e.g., cotton boll-weevil) for many years because of its relatively low phytotoxicity, and it apparently found widespread use for insect control on tobacco. Subsequently, it was replaced by synthetic organic insecticides in many of its applications.

As of mid-1971, applications on fruits, particularly apples, were the major use areas; but increasing amounts have been used on grapes in California in recent years.

Lead arsenate was registered in 1971 for use as a growth regulator on grapefruit (to reduce the citric acid content of the juice) and as a herbicide to control crabgrass and other weeds in turf (except around homes).

Potassium arsenate: Production in the US of the synthetic material is believed to be much less than 100 thousand pounds per year.

Apparently, potassium arsenate is not being used commercially at the present time, although it has been reported as being useful in fly baits, for preserving hides, in textile printing and as a laboratory reagent.

Potassium arsenite: Potassium arsenite is reportedly prepared for medicinal uses by the reaction of arsenic trioxide with potassium bicarbonate. Production appears at present to be limited to a very small quantity produced by a few companies specialising in laboratory chemicals and analytical reagents rather than in medicinal chemicals.

Potassium arsenite is available from chemical reagent suppliers in a purified grade. It was formerly available as "Fowler's solution", which was a 1 percent solution in aqueous ethanol. This solution, which was included in earlier National Formularies, was dropped in 1965. Two older references indicated that Fowler's solution was used as a "hematinic and arsenical." It reportedly was used as a medication for chronic myelogenous leukaemia and in the treatment of certain skin lesions (chronic dermatitis in man). In veterinary medicine, it was reportedly used in the treatment of pulmonary emphysema, chronic coughs, anaemia, general debility, and chronic skin diseases of horses, cattle and dogs. No indication was found that potassium arsenite is presently being used in human medicine. Although an interim tolerance level of 2.7 mg/kg of potassium arsenite was established by the US Environmental Protection Agency in May 1972 from residues in the kidney and liver of cattle and horses (resulting from the external use of potassium arsenite), no evidence was found that potassium arsenite is presently used on these animals.

Sodium arsenate: Sodium arsenate is probably made commercially by treating arsenic pentoxide or arsenic acid with sodium hydroxide.

In 1968, US annual production was estimated to be slightly more than the imports, which had averaged 304 thousand pounds during the previous five years.

It is believed that the maor uses of sodium arsenate are in formulated wood preservatives (known as Wolman salts and Boliden salts) and as an insecticide (in ant killers and animal dips).

Sodium arsenate-based wood preservatives are designed to prevent fungal rot and decay of various wood products (except those intended for food or feed containers).

Sodium arsenate is approved for agricultural use in the up to 6.0 percent in bait formulations, for use against ants and for levels of 0.15 percent) in dips and sprays for goats and sheep.

Sodium arsenate reportedly was formerly used in medicine as an "alternative", as an anthelmintic, and in the treatment of chronic skin diseases.

Sodium arsenite: Sodium arsenite is made by reacting arsenic trioxide with sodium carbonate or sodium hydroxide.

The consumption of sodium arsenite in the US at the present time is undoubtedly much less than the 4.5 million pounds reportedly consumed in 1954. Because of its high mammalian toxicity, sodium arsenite is no longer used as a herbicide along railroad right-of-ways, and governmental restrictions in recent years have limited its present market to certain applications to bare ground, in industrial areas, for tree and stump killing and for bark removal.

It is believed that the major application of this material is still for herbicidal and pesticidal purposes, even though it has been gradually replaced in most of these areas by more efficient organic pesticides with lower mammalian toxicity. As of mid-1971, its use in the US has been restricted drastically by government regulations.

Preparations containing very low percentages of sodium arsenite are permitted, however, for ant control.

The next most important use of sodium arsenite is as an inhibitor for the corrosion caused in oil well piping when oil wells are acidised with hydrochloric acid. In 1970 it was reported that one million pounds were being used for this purpose in the US. Organic inhibitors were said to be gradually replacing sodium arsenite, however.

Sodium arsenite reportedly is used as an intermediate in the production of (1) arsenic-containing medicinals; (2) arsenical soaps for taxidermists; (3) copper acetoarsenite (Paris Green, a mosquito larvicide); and (4) copper arsenite. No information was found on the quantity consumed for these products or on the other applications mentioned in the literature for sodium arsenite: wood preservation, pigment usage, high preservation and textile dyeing.

(b) Analytical methods

The three main methods for the analysis of arsenic are spark source mass spectrometry, neutron activation and atomic absorption. According to Morrison (1972) the detection limits for the first two methods cited are $6 \times 10^{-11}$g and $10^{-10}$g, respectively. The detection limits for atomic absorption vary with the sampling system, the most sensitive being a chemical separation unit coupled with the atomic absorption unit. These units are available commercially, and the Jarrell-Ash Company report detection limits of $10^{-10}$g.

Carey (1968) has described a non-instrumental method for the determination of arsenic in organic arsenates.

Care must be exercised in all methods of analysis that arsenic is not lost by volatilisation.

(c) Occurrence

Arsenic:

Natural environment: The occurrence of elemental arsenic in the environment is believed to be very small compared to the amount of arsenic occurring in other forms (usually the pentavalent state). In these forms, arsenic constitutes 7-11 percent of the gold ores of Sweden and 2-3 percent of lead and copper ores. It is also found in the ores used in tin smelting, zinc refining and cobalt smelting.

Arsenic is widely distributed in the earth's crust. Water leaching, plant uptake and volcanic activity continue to keep arsenicals widespread in the environment.

Arsenic is present in the phosphate rock used to manufacture fertilizers and detergents.

Tobacco smoke: Arsenic derived from insecticides has been detected in small quantities in tobacco smoke (Holland et al., 1959).

Water: In some parts of the world (e.g., Formosa; Province of Cordoba, Argentina) the levels of inorganic arsenic in water have been found to be higher than elsewhere. In a survey on well water made in 1938 in the Province of Cordoba, Argentina, concentrations of the order of 0.0003 percent arsenic trioxide and 0.0005 percent sodium arsenite were found (Arguello et al., 1938).

It has been suggested that fertilizers and detergents manufactured from phosphate rock containing arsenic contribute to the increased arsenic content of river water. For example, in Kansas this was found to be 3-8 µg/kg of arsenic (Angino et al., 1970). The tolerances of arsenic in drinking water given by the US Public Health Service are 10 µg/kg (recommended) and 50 µg/kg (mandatory).

Food: Arsenic can be present in food as a contaminant or as a residue of lead or calcium arsenate used as insecticides, particularly on potatoes and fruit. Arsenic was found in 3.2 percent samples of food items examined in the US during a market-basket survey; residues ranged between 0.1 and 4.7 mg/kg (Cummings, 1966). The daily intake of arsenic (as arsenic trioxide) in the same country was calculated to be 0.137-0.330 mg/person (Duggan and Lipscombe, 1969). Other sources indicate that arsenic is present in the diet at levels of 0.05-0.16 mg/kg (referred to wet weight), this corresponding to an intake of 0.15-0.40 mg/person/day (Schroeder and Balassa, 1966; Somers & Smith, 1971).

Arsenic pentoxide: Arsenic pentoxide does not occur as such in nature. Although it may appear in waste streams from where it is produced or used in manufacture, a more probable source of significant quantities is the runoff from cotton fields where it has been used as a defoliant.

Arsenic trioxide: Arsenic trioxide occurs in nature as the mineral arsenolite ($As_4O_6$). Since arsenic trioxide is formed when arsenic-containing ores are roasted, it may occur as a pollutant in the waste gases and waste waters from ore refineries. Other potential sources include the plants where it is further refined and the many operations in which it is used (pesticide synthesis, glass manufacture, etc.).

Calcium arsenate: Calcium arsenate does not occur in nature as such. It is relatively insoluble, and the presence of excess calcium hydroxide is said to retard its decomposition to water-soluble products. Consequently, it probably would not be readily dissolved in lakes, ponds, streams and ground water supplies. It readily becomes fixed in the soil when used as a pesticide.

Calcium arsenite: Calcium arsenite does not occur as such in nature.

Lead arsenate: Lead arsenate occurs in nature as the mineral shultenite. Since lead arsenate is relatively insoluble in water, it probably would not be readily dissolved in lakes, ponds, streams and ground water supplies. However, lead arsenate does accumulate in the soil. Soils in apple orchards are said to have built up high levels of arsenic as a result of repeated applications of lead arsenate.

Potassium arsenate: Potassium arsenate does not occur as such in nature.

Potassium arsenite: Potassium arsenite does not occur in nature.

Sodium arsenate: Sodium arsenate does not occur as such in nature. However, its major applications (wood preservatives and ant killers) probably offer opportunities for sodium arsenate to accumulate in the soil and appear in the run-off from this soil.

Sodium arsenite: Sodium arsenite does not occur as such in nature. It may be present in the run-off from land that has been kept free of vegetation by the use of sodium arsenite as a soil sterilant.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Many studies have given essentially negative results, but most of them are not referred to in this monograph because of inadequacies in the experimental design (e.g., too few animals, too short a duration, poor survival, too low a level of exposure).

Adequate oral studies on arsenic trioxide in the mouse and on lead arsenate, calcium arsenate, sodium arsenate, arsenic trioxide and sodium arsenite in the rat gave negative results.

The studies designed to detect cocarcinogenicity to mouse skin by potassium arsenite, sodium arsenate or arsenic trioxide gave negative results.

The two recent preliminary reports suggesting possible carcinogenic effects in mice exposed to sodium arsenate, potassium arsenite and arsenic trioxide by subcutaneous, intravenous, oral and transplacental routes are difficult to interpret on the basis of the findings presented, and the results await confirmation.

## 4.2 Human data

The available studies point consistently to a causal relationship between skin cancer and heavy exposure to inorganic arsenic in drugs, in drinking water with a high arsenic content, or in the occupational environment.

The risk of lung cancer is clearly increased in certain smelter workers who inhale high levels of arsenic trioxide. However, the causative role of arsenic is uncertain, since the influence of other constituents of the working atmosphere cannot be determined. An increased relative frequency of deaths from lung cancer has been found in other occupational groups exposed to high levels of inorganic arsenic compounds (e.g., sheep-dip workers, certain mining and vineyard workers).

Cases of lung cancer occurring after the medicinal use of inorganic arsenic compounds, and of liver haemangioendothelioma following various kinds of exposure to arsenic have been reported, but these may be chance associations.

No evidence exists that other forms of cancer occur excessively with heavy arsenic exposure.

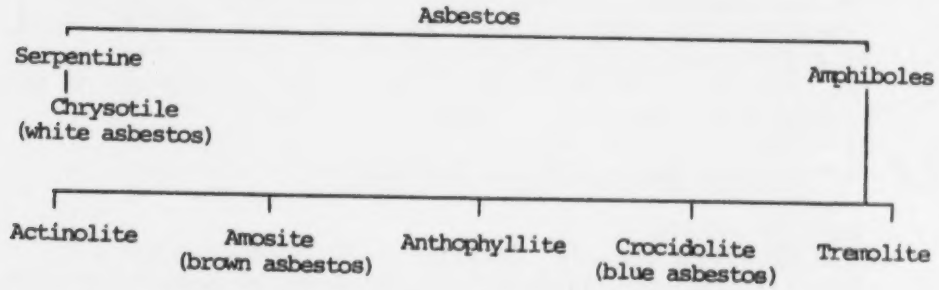
# Asbestos

## 1. Chemical and Physical Data

Asbestos was previously evaluated in October 1972 (IARC, 1973). Since that time new published data became available which were considered by a Working Group especially convened in 1975. The present Working Group has made a final evaluation of all available data published or accepted for publication up to December 1976.

## 1.1 Chemical and Physical Data

Asbestos is the generic name used for a group of naturally occurring mineral silicate fibers of the serpentine and amphibole series. Government agencies in various countries, and industrial groups, currently characterize six fibrous silicates as 'asbestos' (Speil & Leineweber, 1969; US Department of Labor, 1975): the fibrous serpentine mineral chrysotile and the fibrous amphiboles actinolite, amosite, anthophyllite, crocidolite and tremolite.




Current usage of the term asbestos is restricted to these specific silicates, although there are many minerals with fibrous crystal habits that occur naturally. These latter mineral species, however, either do not possess such properties traditionally ascribed to asbestos as, for instance, heat stability, thermal and electrical insulation, the ability to be woven, stability in acids or alkalis, or do not occur in sufficient concentrations for exploitation. The original definition of the word asbestos is derived from the Greek, 'incombustible'.

## 1.2 Synonyms and trade names

| | | |
|---|---|---|
| Chem. Abstr. Reg. Serial No.: | 1332-21-4 | Asbestos fibre<br>Asbestos |
| | 12001-29-5 | Chrysotile<br>Serpentine; 7-45 asbestos;<br>Avibest C;<br>Cassiar AK;<br>Calidria RG 144;<br>Calidria RG 600 |
| | 17068-78-9 | Anthophyllite<br>Azbolen asbestos<br>Ferroanthophyllite |
| | 13768-00-8 | Actinolite |
| | 12172-73-5 | Amosite<br>Mysorite |
| | 12001-28-4 | Crocidolite |
| | 14567-73-8 | Tremolite<br>Silicic acid, calcium magnesium salt (8:4) |

## 1.3 Chemical and physical characteristics

### (a) Chrysotile

(i) Atomic structure: On the basis of powder diffraction and single crystal X-ray crystallographic studies and transmission electron microscopic and selected area electron diffraction investigations, chrysotile has been shown to be a curled sheet silicate, spiralled as a helix around a central capillary (Clifton et al., 1966; Huggins & Shell, 1965; Jagodzinski & Kunze, 1954a,b; Kalousec & Muttart, 1957; Pundsack, 1956; Whittaker, 1963a; Yada, 1967; Zussman et al., 1957).

Chrysotile is the fibrous member of the serpentine mineral group, possessing a rolled trioctahedral clay structure; it is the magnesium analogue of kaolinite (Deer et al., 1962). Half of chrysotile

sheet silicate is composed of planar-linked silica tetrahedra in a pseudo-hexagonal arrangement. Here, all three oxygens at the base of the tetrahedra are shared in a common plane. All unshared apical oxygens in this sheet 'point' in a single direction, above the plane, towards an adjoining 'brucite' layer, which is composed of magnesium ions coordinated octahedrally with oxygen and hydroxyl groups. Two of the three apical oxygens in the tetrahedral sheet replace hydroxyl groups to form the brucite layer. The complete, single chrysotile structure consists of a 1:1 sheet structure of silica and brucite, joined by shared tetrahedral apices. The distance between adjacent composite sheets is in the order of 7.3 mm, with symmetry element repeat every two sheets, or 14.6 nm. The dimensions of the brucite sheet (5.4 nm x 9.3 nm) and the silica tetrahedral sheet (5.0 nm x 8.7 nm) indicate that these basic units are structurally mismatched. There are several mechanisms by which the sheets may 'change' in size so that they will 'fit' over each other: (1) the bonds may stretch to fit, producing a misshapen molecular arrangement; (2) smaller ions may enter the octahedral brucite group, or larger ions may enter the tetrahedral silica group, thereby decreasing or increasing the respective sheet sizes; or (3) the structure may be warped, with the larger brucite sheet curling over the smaller 'tridymite' sheet. The latter mechanism (3) appears to be the dominant method of structural accommodation for chrysotile, although the presence of trace metals and marked disorder along specific crystallographic directions suggest that other factors account for some of such accommodation.

The curvature of chrysotile, its misshapen band angles and resultant charge distribution produce a structure that may be considered to be unstable. A comparison of the stability of the different serpentine mineral forms (Nagy & Bates, 1952) clearly demonstrates this.

The charge on the surface of chrysotile in an aqueous medium is controlled by the hydroxyl groups surrounding the magnesium ion. Because of the adsorption of hydrogen ions at the surface, a net positive charge is produced (Speil & Laineweber, 1969). The surface is commonly hydrophilic, so that particles of chrysotile form a stable suspension in water (Pundsack, 1956, 1961).

(ii) Chrysotile crystal polytypes: Curving of chrysotile most commonly occurs around the axis, i.e., the hollow fibre tube axis parallels crystallographic , forming a gridle of axes. The structure of chrysotile is complicated by the different ways in which the composition sheets are stacked. If adjacent sheets are stacked so that magnesium hydroxyl groups are offset in the same direction and successive sheets have the same brucite configuration, the resulting symmetry belongs to the monoclinic system, and the mineral species is termed 'clinochrysotile.' However, stacking of sheets may reverse so that the net displacement is effectively cancelled. This results in a orthorhambic symmetry. This mineral species is called 'ortho-chrysotile.' Another species of fibre, 'para-chrysotile,' is characterized on the basis of its tubular development parallel to the crystallographic axis. This variety occurs only rarely.

Some investigators indicate that electron diffraction patterns of chrysotile fibres yield fibre patterns of both ortho- and clinochrysotiles; i.e., natural chrysotiles are commonly mixtures of polytypes. However, single fibrils appear to be of either one structural type or the other, and single individual fibrils with mixed characteristics have not been observed (Zussman et al., 1957).

(iii) Fibrils and fibres: Electron micrographs show that single chrysotile fibrils are hollow tubes (Clifton et al., 1966; Langer and Pooley, 1973; Langer et al., 1974; Maser et al., 1960; Yada, 1967). Some of these micrographs suggest that there are channels betweeen individual fibrils as well as internal capillaries. The internal capillaries of chrysotile have been studied and their dimensional characteristics recorded: these range from 20-130 nm (Badollet, 1948; Langer and Pooley, 1973; Langer et al., 1974; Maser et al., 1960; Pundsack, 1961; Whittaker, 1963a; Yada, 1967, 1971). Outer fibril dimensions of up to 600 nm (usually 200-300 nm) in width have been reported (Whittaker, 1963a). Some authors have suggested that chrysotile fibril dimensions are different in different geological localities, e.g., Canadian fibrils tend to be larger than South African varieties. Fibril growth appears to be related to the process of crystallization and to both the chemical and physical environment (Bates, 1959);

Bates et al., 1950; Jagodzinski & Kunze, 1954a,b; Kalousec & Muttart, 1957). A more recent paper (Yada, 1967) has demonstrated that within a single mineral specimen the capillary and fibril widths may vary significantly, and the presence of chrysotile fibrils without the central capillary has been demonstrated. Chrysotile fibrils may develop as both 'cone-in-cone' concentric cylinders and as progressive rolled sheet helices spiralling around a central capillary.

(iv) Chemistry

Major oxides: The ideal crystal chemical formula for chrysotile is: $X_6(Si_4O_{10})(OH, O,F,Cl)_8$. X represents octahedrally coordinated cations of the brucite layer. Magnesium most commonly occupies that position up to the available 6.00 sites, although iron, nickel and manganese may be present at up to several tenths of a percent (Table 1). The Si position represents the tetrahedrally coordinated cation of the silica layer and is almost entirely filled by silicon to the hypothetical 4.00 site vacancy. Rarely, aluminum may be present in the structure; the hydroxyl group may in rare instances be replaced by oxygen, fluorine or chlorine. All substitutions are related to original rock type, provenance and conditions of growth.

The chemical composition of chrysotile is uniform in comparison to that of the amphibole asbestos minerals. A comparison of the empirical composition of chrysotile with that of naturally occurring fibres indicates that the latter tend to be 'dirty': some trace oxides are always present. The high $Fe^{2+}$ and $Fe^{3+}$ contents usually result from contamination by magnetite, which is a ubiquitous accompanying mineral phase when the serpentinized rock is an ultramafic type. Calcium oxide reflects serpentine deposits originating from a silicified dolomite.

Minor and trace elements in chrysotile: Ni, Cr and Co have been identified in trace amounts within chrysotile deposits derived from ultramafic (serpentine) bodies (Table 1). Iron is also ubiquitous. Occassionally, other trace metals are observed, but their presence tends to reflect that of trace mineral phases

Table 1

Chemical Composition of Chrysotile (%)

| Oxide | On basis of $Mg_6Si_4O_{10}(OH)_8$ | Canadian (avg.) (Gaze, 1965) | Shabani, S.Afr. (avg.) (Harington, 1965) | Chrysotile (avg.)[a] |
|---|---|---|---|---|
| $SiO_2$ | 43.35 | 40.3 | 39.15 | 41.8-42.0 |
| $Al_2O_3$ | | 0.7 | 2.15 | 0.1-0.5 |
| $Fe_2O_3$ | | 1.5 | 1.18 | 0.2-1.3 |
| FeO | | 1.0 | 1.33 | 0.1-1.6 |
| MgO | 43.66 | 42.4 | 40.32 | 41.8-42.8 |
| CaO | | 0.2 | 1.09 | 0-0.1 |
| $Na_2O$ | | | 0.09 | 0-trace |
| $K_2O$ | | | 0.15 | 0-0.1 |
| $SO_3$ | | | | 0-0.1 |
| $CO_2$ | | 0.2 | 0.41 | 0-trace |
| $+H_2O$ | 12.99 | 3.7 | 3.09 | 13.6-14.0 |
| | 100.00 | 100.00 | 98.96 | |

Common trace metals detected:

| | | | |
|---|---|---|---|
| chromium | (follows MGFe) | - up to 1000 | µg/g fibre |
| cobalt | (follows Fe) | - up to 1000 | µg/g fibre |
| nickel | (follows Mg) | - up to 5000 | µg/g fibre |

[a] Aboutville, N.Y. (Kalousec & Muttart, 1957); Danville, Quebec (Pundsack, 1956; Pundsack & Reimschussel, 1956); Transvaal, South Africa (Brindley & Zussman, 1957); Gila, Arizona (Nagy & Faust, 1956)

associated with the fibre. For example, high iron content in Canadian fibres may reflect the presence of both ferrian nemalite and/or magnetite (Liebling and Langer, 1972).

The substitution of nickel and iron for magnesium in chrysotile is commonplace in deposits derived from ultramafic rock types (Langer et al., 1972a,b; Morgan and Holmes, 1970; Morgan et al., 1975). Such deposits provide the bulk of chrysotile fiber to the world market.

(v) Impurities

Common mineral impurities associated with chrysotile: There are a large number of rock types which may be precursors of, or associated with, serpentine bodies. These include dunite, dolomite, gabbro, hornblendite (amphibolite), norite, peridotite, picrites and pyroxenite (Deer et al., 1962; Johanses, 1937). Alteration of these rocks to serpentine, accompanied by the formation of lizardite, antigorite and chrysotile, may also include the survival of pre-existing mineral phases. Rock-forming minerals such as olivine and pyroxene may survive the alteration process and contaminate the final mineral fibre. Occasionally, nemalite, tremolite, anthrophyllite and a number of other fibrous mineral phases may be associated with the serpentine body. Ore minerals, e.g., niccolite (nickel arsenide), cobaltite (cobalt arsenide sulphide), arsenopyrite (iron sulphide arsenide) chromite (chromium oxide) or magnetic (iron oxide) may often be present in quantities sufficient to form exploitable mineral deposits. Geological literature is replete with reports of the association of such ore deposits with a serpentinized host rock. Therefore, chemical and minerological data may suggest not only elemental substitutions within the chrysotile structure but more commonly associated trace mineral phases as well.

Chrysotile fiber that has originated from serpentinized dolomites is often contaminated with the carbonate mineral, calcite (Deer et al., 1962; Diller, 1919; Huggins & Shell, 1965). As with the chrysotile fiber originating from ultramafic rock types, the number of associated contaminant phases in carbonate rocks is high. Several papers have listed common minerals and metals associated with chrysotile (e.g., Diller,

1919). Common analytical techniques, generally X-ray diffraction have been used to demonstrate these various mineral associations (Badollet & Gantt, 1965). As in the case of trace metal analysis, trace mineral phases closely follow geological rock type.

The quantities of trace mineral impurities in chrysotile appear to range considerably (Speil & Leineweber, 1969). When present, their particle sizes tend to be extremely small, on the order of a few hundred microns and less (Badollet & Edgerton, 1961). Chrysotiles derived from serpentized dolomites tend to have calcite intergrowths of a size similar to that of magnetite.

Occassionally, the chrysotile fibril itself may contain quantities of amorphous material that is of chrysotile composition but not necessarily the same molecular proportions. For example, it has been noted that the progressive leaching of chrysotile with distilled water may yield what appears to be the mineral phase alpha-sepiolite (Hargreaves & Taylor, 1946).

Hydrocarbon traces: Adsorption of hydrocarbons onto the chrysotile surface has been documented (Harington, 1965); Harington & Roe, 1965). Natural organic contamination is far less common in chrysotile than in crocidolite and amosite, but contamination during industrial fabrication is apparently more widespread than previously thought. Storage of fibre in various containers is one such source of hydrocarbon contamination (Commins & Gibbs, 1969).

Impurities added during preparation: Occasionally, impurities such as nickel-steel fragments are added to the product during the processing of chrysotile asbestos. These are apparently the result of abrasion of machinery by the mineral impurities. The amounts of such steel particles are generally small (Ayer & Lynch, 1967; Badollet, 1952). Hammer milling may increase considerably the nickel, chromium, cobalt and iron content (Badollet & Edgerton, 1961).

(vi) Harsh and soft chrysotiles: It has been recognized on the basis of field observation that the serpentine mineral chrysotile occurs naturally with a range of physical properties. There appear to be differences in the relative flexibility of chrysotile fibres

derived from different geological localities; these have been termed 'harsh' and 'soft' fibres (Speil & Leineweber, 1969).

The relative flexibility and 'feel' of the fibre bundle has been used to distinguish between these types (Dana & Ford, 1957). Although the terms 'harsh' and 'soft' have been applied to certain fibre types to suggest extreme characteristics, fibres generally occur as gradations between these mineral end-types (Badollet, 1948). Occasionally, fibre bundles are observed that do not flex readily, that possess characteristics of harsh fibre types, but that are not truly harsh. These tend to be fibre bundles of chrysotile intergrown intimately with mineral impurities. For example, Canadian fibre tends to possess intergrowths of magnetite and nemalite parallel to the fibre axis. Although these fibres appear to be harsh in the hand specimen, removal of the fibres from the mineral matrix produces a soft flexible mineral species. A summary of recognized properties of these fibre types is given in Table 2.

The nature of the fibre bundle and the mechanical ease of reducing such fibres to the individual fibrils are directly related to the relative degree of harshness or softness. Soft fibres tend to break open easily, producing a large surface area, which permits leaching of magnesium from the exposed fibre surfaces, increasing solution conductivity (Table 2). The relative degree of fibril disorientation may be measured by variations in selected area electron diffraction patterns (Langer et al., 1974).

(vii) Other properties: The chemical stability of chrysotile is limited. When it is in contact with dilute acids or even with solutions at pH of less than 10.8, magnesium tends to be removed from the fibre surface (Hargreaves & Taylor, 1946). On a comparative basis, the stability of chrysotile is generally much less than that of the other serpentine minerals (Nagy & Bates, 1952). Magnesium loss *in vivo* has been demonstrated by both electron microprobe analysis of fibres in tissues and by studies of neutron-activated fibres released in laboratory animals (Langer et al., 1972a,b; Morgan & Holmes, 1970; Morgan et al., 1975). Chemical degradation is accompanied by physical degradation as well (Jaurand et al., 1976).

## Table 2. Characteristics of Soft and Harsh Chrysotile

| Property | Soft fibre | Harsh fibre | Reference |
|---|---|---|---|
| FIBRE BUNDLE | | | |
| Feel | Smooth, silky | Harsh, splintery | Badollet, 1948 |
| Tenacity (Flexibility) | Flexible, may be bent to >90° without rupturing | Still, ruptures at <90° | Badollet, 1948 |
| Size reduction (length) | Poor, resists fibre axis break | Good, easily broken across fibre axis | Badollet, 1948 |
| Fibrilization of bundle | Excellent to good, easily opened | Poor, tends to remain in tight bundles | Badollet, 1948 |
| Surface areas (equal amount of materials identically size-reduced) | Average Canadian sample: 23 $m^2/g$; some as high as 30 $m^2/g$ | Average harsh: 11 $m^2/g$; some as low as 4 $m^2/g$ | Badollet & Streib, 1955 |
| INDIVIDUAL FIBRILS | | | |
| Appearance under electron microscope | Fibrous, thin filaments, moderately translucent | Lath-like, electron-dense bundles | Badollet, 1952; Bates, 1958; Zussman et al., 1957 |
| Individual fibrils | Empty to partially filled capillary | Filled capillaries | Zussman et al., 1957 |
| Electron diffraction pattern | Around reflections, disordered inter-fibril relationships | Single round or streamlined reflections, ordered inter-fibril relationships | Badollet, 1952 Zussman et al., 1957 |
| PHYSICAL PROPERTIES (BULK SAMPLE) | | | |
| Porosity | High | Low | Badollet, 1948 |
| Filter rates | Slow | Fast | Badollet, 1948 Badollet & Streib, 1955 |
| Filtrate clarity | Clear | Cloudy | Badollet, 1948 |
| Conductivity (2.9% suspension) | Average Arizona soft: 22.2 $ohms^{-1}cm^{-1}(x10^5)$ | Average Arizona harsh: 11.9 $ohms^{-1}cm^{-1}(x10^5)$ | Pundsack & Reimschussel, 1956 |
| Mg leach (% NaCl equivalent) | 0.27 | 0.10 | Pundsack & Reimschussel, 1956 |
| CHEMICAL PROPERTIES (BULK SAMPLE) | | | |
| Structural water (dry weight) | 12.5-14.5% | 11.0-12.5% | Badollet & Streib, 1955 |
| CaO content | Trace to nil (Arizona soft) | Trace to minor oxide (Arizona harsh) | Diller, 1919 Pundsack & Reimschussel, 1956 |
| $Al_2O_3$ content | Trace to minor oxide (Arizona soft) | Trace to nil (Arizona harsh) | Diller, 1919 |

The physical stability of chrysotile is also limited. Chrysotile appears to lose its crystalline character when its size is reduced beyond a certain range. This can be observed after chrysotile is ball-milled for periods of more than 60 seconds (Langer et al., 1977). These structural changes can be followed by means of X-ray diffraction and infra-red spectographic and other techniques. Mechanical energy first breaks the physically weak chemical bonds; chrysotile is initially disrupted along the stacking direction, as indicated by a loss of the (h0l) reflections (Brindley & Zussman, 1957).

This is of particular importance in terms of interpreting biological data in which animal experimentation is carried out using materials which have been ball-milled for size reduction. It has been shown that ball-milling results in decreased haemolytic activity and in the activation of free radicals on chrysotile surfaces (Langer et al., 1977).

A range in the densities of natural chrysotile fibres has been observed: values for Arizona chrysotiles, derived from serpentized dolomites, have been reported to be between 2.19 and 2.25 g/ml (Huggins & Shell, 1965); the density of chrysotile from Canada has been shown to be approximately 2.56 g/ml (Kalousec & Muttart, 1957; Pundsack, 1956). These reported ranges in density of chrysotile have been attributed both to mineral impurities and to the presence of magnesium silicate material that 'stuffs' the central capillaries and fibril interstices in the fibre bundle.

Chrysotile has also been shown to possess paramagnetic properties, which can be used to produce alignment of fibres for counting and sizing (Timbrell, 1975).

(viii) The wide geological distribution of serpentine rocks; chrysotile as a contaminant: Chrysotile asbestos is mined as a non-metallic ore; however, the mineral itself is far more widespread than previously thought. For example, serpentine belts are associated with nearly every major mountain chain axis around the world (Hess, 1955), and serpentine is a common host rock for some ore deposits (Bateman, 1959). It has been shown that naturally occurring serpentine consists of mixtures of chrysotile and of antigorite (Nagy & Faust, 1956) and the platy phase

lizardite (Brindley & Zussman, 1957). Therefore, exposure to chrysotile may come from a variety of rock types in which chrysotile itself is not being mined as such. A number of fibrous minerals may be interdispersed with or associated with chrysotile, for example, amphibole asbestos varieties (Table 3) (Langer et al., 1971; Pooley, 1976).

(b) Amphibole asbestos minerals The amphibole asbestos minerals are each as complex as chrysotile. The following descriptions are offered as an outline, and a table is provided for direct comparison of the different mineral species (Table 4).

(i) Atomic structure: The amphibole minerals are structurally inosilicates, double-chains, cross-linked with bridging cations. The structure is formed by co-planar sharing of two of three oxygens at the base of the silica tetrahedra, which extends as a single chain along an indefinite axis. The double-chain is completed by the third oxygen, which is shared between two tetrahedra of opposite, facing chains. These units form the asbestos fibre axis (Deer et al., 1967; Ernst, 1968; Whittaker, 1960, 1963b).

The different amphibole asbestos fibres possess this basic structure, with small modifications brought about by chemical variation. Cation substitutions within the amphibole structure modify interplanar spacings and the stacking angle of chain units, referred to as the beta angle. This angle forms the inclined place of monoclinic structures. Unit cell dimensions and beta angles are obtainable from any number of reference sources (Deer et al., 1967; Whittaker, 1960, 1963b). A review of such properties, e.g., space group symmetry, is given in Table 5.

(ii) Chemistry: The complexity of the amphibole asbestos minerals can be illustrated by a brief and general description of amphibole crystal chemistry. There are several general chemical structural formulae used for all amphibole minerals: $(WXY)_{7-8}\ (Z_4O_{11})_2\ (O, OH, F)_2$ (Mason, 1958) or, more frequently, $W_{0-1}\ X_2Y_5\ (Si_4O_{11})_2\ (O, OH, F)_2$ (Ernst, 1968). The cations WXY correspond to the structural sites A, $M_1$, $M_2$, $M_3$ and $M_4$. Some confusion generally arises from the description of the chemistry of crystals in

Table 3

Synonyms for serpentine-like rocks, alteration products and minerals that may contain or be associated with chrysotile

| Rocks | Minerals (Faust & Fahey, 1962) | |
|---|---|---|
| serpentine<br>vermiculite<br>talc | antigorite<br>antillite<br>aquacreptite<br>baltimorite<br>bastite<br>bowenite<br>dermatite<br>deweylite<br>hydrophite<br>jenkinsite<br>lizardite<br>marmolite | meerschaum<br>metaxite<br>neolite<br>ophicalcite<br>picrolite<br>picrosmine<br>porcellophite<br>pyknotrope<br>retinalite<br>schweizerite<br>termophyllite<br>williamsite |

Table 4

Amphibole minerals directly or possibly related to asbestos

| Asbestos Type | Asbestiform-related mineral |
|---|---|
| actinolite - tremolite | ferroactinolite<br>garnierite<br>hexagonite<br>richterite<br>triodite |
| anthophyllite | ferroanthophyllite<br>ferrogedrite<br>gedrite |
| crocidolite | crossite<br>glaucophane<br>magnesioriebeckite<br>riebeckite |
| amosite | cummingtonite<br>grunerite<br>kupfferite<br>montasite |

## Table 5

## Mineral relationships and common substitutions of the amphibole asbestos types

| Asbestos fibre | Related mineral system | General chemical formula | Crystal system & space group | Cation in M4 Site | Common cation substitution and resulting mineral |
|---|---|---|---|---|---|
| anthophyllite | anthophyllite-gedrite | $(FeMg_6)Si_8O_{22}(OH)_2$ | orthorhombic Pnma | Mg⇌Fe | Mg ⇌ Fe ferroanthophyllite<br>(Mg,Fe)Si ⇌ Al,Al gedrite<br>(Mg,Si) ⇌ (Al,Al) gedrite<br>(MgSi) ⇌ (Fe,Al) ferrogedrite |
| amosite | grunerite-cummingtonite | $(Fe_6Mg)Si_8O_{22}(OH)_2$ | monoclinic C2/M | Fe⇌Mg | Fe ⇌ Mg magnesio-grunerite cummingtonite<br>Fe ⇌ Mn mangano-grunerite mangano-cummingtonite |
| actinolite-tremolite | actinolite-tremolite | $Ca_2(MgFe_6)Si_8O_{22}(OH)_2$<br>$Ca_2(MgFe_6)Si_6O_{22}(CH)_2$ | monoclinic C2/M<br>monoclinic C2/M | Ca<br>Ca | Fe ⇌ Mg complete gradation: ferroactinolite-tremolite<br>Fe ⇌ Mn tirodite |
| crocidolite | riebeckite-glaucophane | $Na(Fe_7^{3+}Fe_3^{2+})Si_8O_{22}(OH)_2$ | monoclinic C2/M | Na | $Fe^3$ ⇌ Al<br>$Fe^2$ ⇌ Mg complete gradation: riebeckite-glaucophone |

terms of structural accomodations of cations. The interchanged notation for structural and chemical symbols would be expressed as: $(A)_{0-1}$ $(M_4\ M_4)$ $(M_1\ M_1\ M_2\ M_2\ M_3)$ $(Si_4O_{11})_2$ $O,Oh,F)_2$. Therefore, chemistry and structure are interdependent and related to factors such as cation size and valence (Table 6).

Basically the amphibole minerals consist of chain structures, with nine structural sites that may accomodate cations. Any change in ratios of these different cations would change the mineral species. However, for the different asbestos types, there appears to be limited substitution in terms of chemical species and of their locations in the structure (Table 5).

Anthophyllite: Anthophyllite is considered to be an orthorhombic magnesium-iron amphibole with possible aluminium substitution. This mineral species forms a partial solid solution with the mineral gedrite, an aluminium-rich fibre of similar properties (Table 5).

Amosite: Amosite is an exploited variety of grunerite. As part of the grunerite-cummingtonite solid solution series, amosite tends to occur with more iron than magnesium in its structure. Manganese substitution may occur in concentrations of up to 4% by oxide weight (Table 5).

Actinolite and tremolite: Actinolite and tremolite appear to form a solid solution series, representing end-members of that mineral group (Deer et al., 1967). Both mineral species possess calcium in the $M_4$ structural site, with complete iron-magnesium gradations in the $M_1$ through $M_3$ valence sites. Occasionally, managanese substitutes for iron (Table 5).

Crocidolite: Crocidolite is the exploited form of the rock-forming amphibole mineral riebeckite. Riebeckite may change chemically with replacement of $Fe^{2+}$ for magnesium and $Fe^{3+}$ for aluminium (Table 5). For example, magnesio-riebeckite is mined as crocidolite in Bolivia (Speil & Leineweber, 1969).

The chemical contents of the amphibole asbestos types are given in Table 7.

## Table 6

## Chemical and structural notations for the amphiboles

| Cation site | Structural notation | Cation coordination | Number of site cations in unit cell | Change of cation | Location in structure | Common elements |
|---|---|---|---|---|---|---|
| W | A[b] | 10 - 12 FCN | 1 | + to ++ | back of 2 opposed chains | Na, X, Li Ca |
| X | M4 | 6 - 8 FCN | 2 | + to ++ | edge of 4 adjacent chains | Na, K Ca, Mn, Fe, Mg |
| Y | $M_1$,$M_2$,$M_3$ | 6 FCN | 5 | ++ to +++ | front of 2 facing chains | Fe, Mg, Ti Fe, Al[c] |
| Z | $Si_I$, $Si_{II}$ | 4 FCN | 4 | +++ to ++++ | forming single chain unit | Al Si[d] |

[a] Ordering of size of sites: $M_4 > M_3 > M_2 > M_1$

[b] A-sites frequently vacant; if $M_4 > 2$, A-site is filled (Whittaker, 1960)

[c] Y-sites can also be filled by Mn, Cr, Li, Zn

[d] Al substitutes for Si at up to 1 in 4

Table 7

Chemical range of the asbestos types [a]

| | Amosite | Anthophyllite | Crocidolite | Actinolite | Tremolite |
|---|---|---|---|---|---|
| $SiO_2$ | 49-53 | 56-58 | 49-53 | 51-56 | 55-60 |
| $Al_2O_3$ | - | 0.5-1.5 | 0-0.2 | 1.5-3 | 0-2.5 |
| $Fe_2O_3$ | - | - | 17-20 | 0-3 | 0-0.5 |
| FeO | 34-44 | 3-12 | 13-20 | 5-15 | 0-4 |
| MgO | 1-7 | 28-34 | 0-3 | 15-20 | 21-26 |
| CaO | - | - | 0.3-2.7 | 10-12 | 11-13 |
| $Na_2O$ | trace | - | 4-8.5 | 0.5-1.5 | 0-1.5 |
| $K_2O$ | 0-0.4 | - | 0-0.4 | 0-0.5 | 0-0.6 |
| $H_2O$ | 2.5-4.5 | 1-6 | 2.5-4.5 | 1.5-2.5 | 0.5-2.5 |
| Common trace elements Ag, Ba, Ce, Co, Cr, Cu, Li, Mn, Mo, Nb, Ni, Sc, Sr, Th, V, Zr | | | | | |

[a] Based on superior analyses of Museum quality representative fibres

(iii) Minerals similar to the amphibole asbestos types: Because of the complexity of the structure of the amphiboles and the wide range of possible cation substitutions in terms of size and valence, it is important to note that a number of minerals should be regarded as akin to asbestos types. Table 4 includes a partial list of rock-forming minerals which may form fibres that possess properties similar to those of amphibole asbestos types occurring in exploited areas.

(iv) Physical properties: The biological activity of the amphibole asbestos types is possibly related to physical properties as well as to chemical properties. The wide variation in chemical structure of the amphibole varieties suggests that biological activity is not restricted to any one chemical variety (Langer et al., 1974; Pooley et al, 1970; Timbrel et al., 1970). For example, crocidolite tends to form thinner fibres than amosite; in general, amosite tends to form thinner fibres than anthophyllite. Diameter is the determining factor in the ability of a fibre to penetrate the lung airways.

The surface charges of all of the amphibole asbestos fibres are negative in aqueous media (Prasad & Pooley, 1973). The magnitude of the surface charge is different for each of the different fibre types. Stability in alkaline and acid environments also varies considerably and has been studied in detail (Speil & Leineweber, 1969).

The earth's crust, a complex of multiple rock types, is composed primarily of silicate minerals (Wahlstrom, 1956). Although the physical and chemical natures of these rocks vary greatly (Poldervaart, 1955), perhaps only six mineral groups constitute the 'rock forming assemblage' (Wahlstrom, 1956), classified on the basis of their atomic structures and chemistry. It is of great importance to note that chrysotile, the asbestos fibre used most widely throughout North America, is not considered to be an 'abundant' mineral phase. Rather, almost 8% of the earth's crust is composed of amphiboles (Wahlstrom, 1956). Since most of the asbestos fibre types are members of that mineral class, this fact is of particular importance. Asbestos terminology is not commonly used to describe the rock-forming counterpart; therefore, one might suspect that many mining areas

of the world represent sources of potential asbestos exposure and disease because of their content of these fibrous gangue minerals (see section 3.4c).

## 2. Production, Use, Occurrence and Analysis

### 2.1 Production and use

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited (Hendry, 1965); Hueper, 1965). During the next 50 years there were gradual increases in production and use: a cumulative total of somewhat less than 5000 million kg had been mined by 1930.

World population has accelerated over the past four decades (Table 8); for example, world mine production increased by 50% between 1964 and 1973. In the latter year, the two major producing countries were Canada (sales were 1790 million kg) and the USSR (estimated production, 1280 million kg); other countries with significant mine production were the Republic of South Africa, Rhodesia, the People's Republic of China, Italy and the USA (US Bureau of Mines, 1975).

Table 8
World production of asbestos

| Year | World production (million kg) | % Canada | % USSR |
|---|---|---|---|
| 1960[1] | 2 210 | 45 | 29 |
| 1970[2,3] | 3 490 | 44 | 30 |
| 1973[2] | 4 093 | 41 | 31 |
| 1974[2] | 4 115 | 40 | 33 |
| 1975[4] | 4 560 | 23 | 48 |
| 1976[4] | 5 178 | 29 | 44 |

[1] From May, 1965
[2] From Clifton, 1974
[3] From Clifton, 1972
[4] From Fagan, 1976

Most asbestos is used in the construction industry, in general, accounting for two-thirds of the usage. Over 3000 uses of asbestos have been identified (Rosato, 1959); important uses include asbestos cement sheets and pipes, insulation materials, taping compounds and floor and ceiling tiles (Hueper, 1965) (see also Table 9). The asbestos content of a product is not necessarily an indication of its relative health risk, for in many products the fibres are tightly bound to the matrix or are encapsulated. A potential health risk arises when asbestos fibres are set free, e.g., during the drilling or sawing of asbestos cement sheets.

Friction materials constitute an important class of asbestos materials. These include not only clutch facings and brakes for cars, lorries, railway carriages and aeroplanes but also braking materials widely used in industry for machinery. Asbestos-containing gaskets are also often used.

Insulation materials often contain asbestos. Asbestos materials have been applied in blocks, or pipe-sections, or as asbestos cement, or sprayed on in compounds which often contain rock wool, binders and other agents. Sprayed asbestos materials are used for decorative and acoustic purposes, as well as for the fireproofing of structural elements in buildings.

An extraordinary variety of other uses of asbestos are known, ranging from papier mache materials used by school children and fireproof clothing and gloves to fillers for plastics. Such uses may be found to have considerable impact in terms of public health terms, since large numbers of people may be exposed. The same perspective may be valid in considering end-product use of asbestos materials, especially in the construction industry or in shipbuilding and ship repair. A single insulation worker, cutting asbestos block or mixing asbestos cement, may cause the exposure of many other workers roundabout, e.g., electricians, plumbers, masons, bricklayers, sweepers and others. The importance of such 'bystander' exposure has been emphasized by the observations of Harries (1976) and Skidmore & Jones (1975).

Tremolite is not at present exploited as an asbestos mineral in its own right. Materials that include tremolite as a major component are, however, produced in many parts of the world. These include many industrial powders referred to as talcs or tremolitic talcs (Pooley & Rowlands, 1977); Rohl et al., 1975).

Table 9[a]
Asbestos distribution by end use, grade and type in the US, 1974
(million kg)

| | Chrysotile | Crocidolite | Amosite | Anthophyllite | Total |
|---|---|---|---|---|---|
| Asbestos cement pipe | 168 | 33 | 0.9 | 0.18 | 202 |
| Asbestos cement sheet | 82 | | 3.9 | | 86 |
| Flooring products | 139 | | | | 139 |
| Roofing products | 66 | | 1.5 | | 67 |
| Packing & gaskets | 26 | 0.09 | | | 26 |
| Insulation, thermal | 6.6 | | 1.6 | | 8 |
| Insulation, electrical | 4.2 | | | | 4 |
| Friction products | 72 | | | 0.18 | 72 |
| Coatings & compounds | 34 | | | | 34 |
| Plastics | 15 | 0.18 | | 0.63 | 16 |
| Textiles | 18 | | | | 18 |
| Paper | 57 | 0.18 | | | 57 |
| Other | 33 | 0.36 | 0.45 | | 34 |
| Total | | | | | 763 |

[a] From Clifton, 1974

Anthophyllite is a talc-like form of asbestos; it is used as an industrial talc and in paper-processing, plastic products, asbestos cement pipes and friction materials (Clifton, 1974). Other uses are described by Rosato (1959).

Known commercially exploited deposits

Chrysotile: The largest commercial deposits of this mineral are in the USSR and Canada. It is also mined in the People's Republic of China, Cyprus, Italy, southern Africa and the USA. Recently, an open-pit mine has begun production in Australia. In the past, small amounts were mined in Corsica (Boutin et al., 1976).

Crocidolite: Most of this fibre comes from the northwestern Cape and Transvaal areas of South Africa. In the past, small amounts were mined in western Australia (Wittenoom Gorge) and Bolivia (Chichabamba).

Amosite: Transvaal, South Africa, is the main source of this type of fibre. An identical fibre has been found in India and will be produced under the name of mysorite.

Anthophyllite: This form of asbestos was exploited in Finland until 1974; the smaller quantities are found in a number of other countries. It is a common contaminant of talc deposits in the US (Kleinfeld et al., 1974; Pooley & Rowlands, 1977; Rohl et al., 1975).

Tremolite: Some limited mining of tremolite fibres was carried out in the US and in the Far East. The fibre now exists primarily as a natural contaminant in other exploited materials, e.g., talc (Kleinfeld et al., 1974; Pooley & Rowlands, 1977; Rohl et al., 1975).

## 2.2 Occurrence

The occurrence of asbestos in the general or occupational environment has been reported in various units of measurement; in workplaces, air units include million particles per cubic foot (mppcf) or, more recently, number of fibres > 5 µm per ml and million fibres per $m^3$; in ambient air samples, values are generally recorded on a gravimetric basis, e.g., $ng/m^3$.

It would be desirable to have a conversion factor in order to relate ambient asbestos levels to occupational levels; however, attempts to formulate such a conversion factor have

generally been unsuccessful because of large variability (NIOSH, 1977). This is to be expected, as ambient levels are generally determined by transmission electron microscopy, whereas phase contrast optical microscopy is used to measure occupational exposures. In addition, techniques used to prepare samples for electron microscopic observation may cause alterations in fibre size (diameter and length) distributions. However, the direct transfer technique may overcome these difficulties (Sebastien et al., 1976a).

Measurements of asbestos in fluids, including water, beverages, etc., have beem expressed as fibres per ml, fibres per l or ng per g of sample. For more details concerning the problems in detecting asbestos, see section 2.3.

(a) Asbestos in the General Environment

Air: Concentrations not exceeding 100 ng/$m^3$, and usually less than 10 ng/$m^3$, asbestos fibres are present in the general urban atmosphere (Holt & Young, 1973; Nicholson & Pundsack, 1973; Sebastien & Bignon, 1974; Sebastien et al., 1976a; Selikoff et al., 1972a). However, concentrations of 10-5000 ng/$m^3$ asbestos fibres have been reported near some factories using asbestos (Nicholson et al., 1975; Rickards, 1973).

Contamination of the air inside buildings can occur from damage or erosion of asbestos-sprayed materials or from working with asbestos-containing materials. Nicholson et al. (1975) found, in in 19 buildings investigated, values ranging from 2-200 ng/$m^3$. Sebastien et al. (1976a) found levels as high as 800 ng/$m^3$.

In an elementary school in the US with a spray-formed, domed asbestos roof, asbestos fell intermittently to leave dust on the surface of the furniture. The intake filters of the ventilation system which recirculated the school-room air were clogged with asbestos fibres, and personal samplers on school children showed that up to 3.8 asbestos fibres greater than 5 µm in length per ml of air occurred within the school (US Department of Health, Education, and Welfare, 1972a; Young, 1972).

Levels of asbestos fibre contamination in buildings appear to be related to the application process used on interior surfaces (Nicholson et al., 1976). 'Dry' processes, in which no liquid is added to matrix binders, tend to deposit the insulation material as a loose 'fluff'. This material disintegrates on touch and cannot withstand the abrasion of air movement.

The lengths and diameters of asbestos fibres found inside such buildings are similar to those described by Gibbs & Hwang (1975) for fibres sampled in various work environments (Sebastian et al., 1976a). In both situations, the percentage of fibres with diameters less than 0.5 µm and with lengths greater than 5 µm was about 20% for amphibole and 1% chrysotile.

Table 10 indicates various exposure levels in the air to which the general population may be exposed.

Table 10
Examples of exposure levels in air [a]

| Exposure | Asbestos Concentration ($ng/m^3$) | |
|---|---|---|
| | USA | Paris |
| Ambient air (urban) | 0.1-100 | 0.1-10 |
| Buildings sprayed with asbestos | 0.1-800 | 0.1-800 |
| Near asbestos spraying | 10-1000 | - |
| Near asbestos factory | 10-5000 | 10-3000 |

[a] From Nicholson et al. (1975) and Sebastien et al. (1976a)

The presence of asbestiform minerals in non-commercial deposits is widespread in many geological formations; the fact that fibres can be released when the rocks are crushed provides a further source of contamination (for discussion of other fibrous minerals, see section 3.3 d). In this regard, the use of asbestos mine tailings on roads may prove to be an important hazard to the general public, and the use of asbestos-containing, quarried, crushed rock may also be a potential risk. This question was raised in a recent community survey of lung cancer (Newman et al., 1976). Similarly, the use of asbestos stucco, employed as cladding for buildings, may result in environmental exposure. The incipient danger from discarded asbestos is

indicated by the findings of 60-100 million asbestos fibres/$m^3$ in the ambient air in the vicinity of waste dumps (Harwood & Blaszak, 1974).

Water: Average concentrations of asbestos in drinking-water ranged from 0.3 to 1.5 µg/l as measured in eastern US river water (Nicholson & Pundsack, 1973). Levels of 2-173 million fibres/l were found in Canadian tap-water, the highest levels being found in unfiltered tap-water near a mining area (Cunningham & Pontefract, 1971).

Levels up to 12.46 µg/l chrysotile asbestos, as determined by electron microscopy, were found in the Jumata and Connecticut rivers (American Water Works Association, 1974). A study of the Great Lakes and St. Lawrence River bywaters showed average concentrations of about 1.7 million asbestos fibres/l. Locations with higher counts were found along the north shore of Lake Superior between Silver Bay and Duluth, along the St Clair River, downstream from Montreal, and in the asbestos mining district in the province of Quebec (Cook et al., 1974; Zielhuis, 1977).

Food: The asbestos contents of food have not been well investigated; asbestos filters and talc, which may contain asbestos as an impurity, may be used in the manufacture of processed foods, e.g., sugar, vegetable oil, lard and coated rice (Merliss, 1971; Wolff & Oehme, 1974).

Beverages: Asbestos fibrils, considered to be chrysotile, at levels of 13-24 million fibres/l have been found in samples of one type of spirit probably filtered with asbestos filters (Wehman & Planthold, 1974).

Biles & Emerson (1968) and Cunningham & Pontefract (1971) also reported the occurrence of asbestos fibres in British, Canadian and American beer (1-6.6 million fibres/l). Asbestos fibres were found in various sherries, ports, vermouths and soft drinks (1.7-12.2 million fibres/l) (Cunningham & Pontefract, 1971).

Pharmaceuticals: Chrysotile asbestos has been found in some samples of parenteral drugs (range 1-1000 ng/g) (Nicholson et al., 1972). In the US, no asbestos-containing or other fibre-releasing filter may be used in the manufacture, processing or packaging of such products, unless it is not possible to manufacture that drug product or component without the use of such a filter (US Food and Drug Administration, 1976).

Dental practice and dental school laboratories: Asbestos-containing periodontal packs are sometimes used after gingival surgery (Infante & Lemen, 1976). In dental schools, asbestos tape is used to hold gold that is heated and then cast into moulds during dental laboratory procedures. This may be a potential problem and has not been evaluated by adequate industrial hygiene monitoring.

(b) Asbestos in the work environment

Asbestos contamination of the air can be caused by spraying of asbestos material either for fire protection or for decorative or acoustical purposes; contamination was found to be high during the application of sprayed mineral fibre (Nicholson & Pundsack, 1973). A comparison of asbestos concentrations in air under different circumstances as measured by electron microscopy is as follows: near asbestos spraying, 10-1000 ng/m$^3$; during a milling operation, 10-5000 ng/m$^3$; in other occupational exposures, 1000->100,000 ng/m$^3$ (Nicholson et al., 1975).

Fibre concentrations in various asbestos-using industries in the US prior to 1971, as determined by optical and electron microscopy, are given in Table 11.

Table 11
Concentrations of fibres in various asbestos-using industries in US before 1971[a]

| Industry | Range of means (fibres > 5 µm/ml) | Range of individual samples (fibres > 5 µm/ml) |
|---|---|---|
| Textile | 0.1-29.9 | 0.0-143.9 |
| Insulation | 0.1-74.4 | 0.0-208.4 |
| Paper packing and asphalt production | 0.2-13.6 | 0.0-18.9 |
| Cement shingles, mill-board and gasket | 0.1-4.4 | 0.0-16.6 |
| Friction | 0.1-14.4 | 0.1-32.4 |
| Cement pipe | 0.2-6.3 | 0.0-13.4 |

[a] From US Department of Health, Education, and Welfare (1972b)

Airborne asbestos sampling programmes do not at present, however, attempt to discriminate between the various fibrous minerals present in dust samples. Table 12 gives a comparison of the length distributions of airborne asbestos fibres, as determined by electron microscopy, in various industries in the US.

Table 13 gives the contents of asbestos fibres, byproducts and fibre type, in asbestos products produced in various EEC countries.

Table 12
Lengths of asbestos fibres in air near various US industries

| Operation | Fibre type | Median length (µm) | % >5 µm |
|---|---|---|---|
| Textile | | | |
| Fibre preparation and carding | Chrysotile | 1.4 | 4 |
| Spinning, twisting, weaving | | 1.0 | 2 |
| Friction | Chrysotile | | |
| Mixing | | 0.9 | 2 |
| Finishing | | 0.8 | 2 |
| Asbestos-cement pipe | Chrysotile | | |
| Mixing | | 0.9 | 2 |
| Finishing | | 0.7 | 1 |
| Pipe innsulation | Amosite | | |
| Pipe forming | | 4.9 | 51 |

Occupational exposure in situations other than the traditional asbestos processes (mining, milling, factory production and handling of asbestos products) has been shown to be of increasing importance. Such exposures occur during end-product use, as among asbestos insulation workers (Selikoff et al., 1964), among brake repair and brake maintenance workers (Lorimer et al, 1976; Rohl et al., 1976, 1977), and as the result of indirect occupational exposures, particularly in ship building and ship repair (Harries, 1968, 1976), and in the construction industry. Other exposures occur in relation to inspection, repair and maintenance work on asbestos-containing structures and equipment, in refineries and

Table 13
Asbestos products and their asbestos contents in EEC countries[a]

| Product | Approx. asbestos content (% wt.) | Asbestos fibre type[b] |
|---|---|---|
| Asbestos-cement building products | 10-15 | C,A,Cr |
| Asbestos-cement pressure, sewage and drainage pipes | 12-15 | C,Cr,A |
| Fire-resistant insulation boards | 25-40 | A,C, |
| Insulation products, including sprays | 12-100 | A,C,Cr |
| Jointings and packings | 25-85 | C,Cr |
| Friction materials | 30-70 | C |
| Textile products not included above | 65-100 | C,Cr |
| Floor tiles and sheets | 5-7.5 | C |
| Moulded plastics and battery boxes | 55-70 | C, Cr |
| Fillers and reinforcements and products made thereof (felts, millboard, paper, filter pads for wines and beers, underseals, mastics, adhesives, coatings, etc.) | 25-98 | C,Cr |

[a] From Zielhuis (1977)
[b] A = amosite; C = chrysotile; Cr = crocidolite (not used in all EEC countries)

chemical plants, buildings, railway locomotives and wagons, shipyards and power plants. Increasingly important exposures can be expected to result from building demolition and waste disposal (US Environmental Protection Agency, 1975). These could pose a considerable problem, in view of the very large amount of asbestos now in place as a result of the cumulative use of the material during the past century. Exposures may also occur during the wearing of asbestos safety garments (Gibbs, 1975), during cleaning operations on buildings formerly sprayed with asbestos (Skidmore & Jones, 1975) and during the handling of bags formerly used in the transport and storage of raw or milled asbestos (US Department of Labor, 1975).

(c) Domestic exposure

Domestic exposure of household contacts with asbestos may occur from dusts brought home on workers' clothes, shoes, hair, equipment, etc. (Anderson et al., 1976); Newhouse & Thompson, 1965; Wagner et al., 1960). Nicholson et al. (1975) found asbestos levels ranging from 100-500 ng/$m^3$ in the houses of workmen.

Other domestic exposures, also widespread, are para-occupational exposures from household repairs and do-it-yourself construction using asbestos-containing materials, such as asbestos cement sheets, plaster fillers and wall-joining compounds (Rohl et al., 1975), furnace and heating equipment cements and other repair materials. Such exposures may increase as more and more householders undertake their own maintenance repairs.

## 2.3 Detection of asbestos

Procedures for the sampling and measurement of airborne asbestos dust by the membrane filter method have been described (Asbestosis Research Council, 1971a,b). These procedures have been evaluated in detail by the National Institute for Occupational Safety and Health (NIOSH, 1977). A report on inter-laboratory comparison of the counting of samples obtained by this method is given by Beckett & Attfield (1974).

Phase contrast-optical microscopy is used in the routine examination of dust samples because of its low cost and speed of performance. However, it can provide only an index of fibre presence and of the size and optical properties of particles that may be used to identify individual fibres. The technique is limited, since only the largest fibres in a sample can be

seen, and, when employed for identification purposes, it is cumbersome and requires an expert microscopist to interpret the results.

X-ray diffraction techniques have been used to establish the presence of asbestos, but they cannot differentiate between the fibrous and non-fibrous forms of these minerals. Quantitative asbestos determination, using X-ray techniques, is complicated by the methods used for sample preparation and by the presence of minerals which may display X-ray reflections in similar positions to those of the asbestos minerals (Keenan & Lynch, 1970; Rohl & Langer, 1974; Rohl et al., 1976). It also requires the preparation of standards for calibration purposes. Minimum detection levels of 2.0% weight for anthophyllite, 0.25% for chrysotile and 0.1% for tremolite have been reported in talc (Rohl & Langer, 1974). The techniques require bulk samples that are not available in most environmental situations.

Differential thermal analysis has been used to determine chrysotile asbestos fibres in bulk talc samples but has not been used for environmental samples. Differential thermal analysis, like X-ray diffraction, is not capable of differentiating between asbestos fibres and their non-fibrous mineralogical polymorphs. A minimum detection level of 1% chrysotile by weight has been reported in talc (Schelz, 1974). This level of contamination has, however, rarely been observed in natural talcs.

Both transmission and scanning electron microscopy have been used to identify and quantify asbestos fibres. The scanning electron microscope can give only morphological information, unless it is fitted with energy or wave-length dispersive X-ray spectrometers with which microchemical analysis of single particles can be performed; this technique was used by Beckett (1973). Transmission electron microscopy is a much more versatile technique, since with this method particle morphology can be accurately observed and electron diffraction patterns are displayed (NIOSH, 1977). Micro-chemical analysis of particles (electron microprobe analysis) can be obtained when the technique is used in conjunction with X-ray analytical equipment (Jaurand et al., 1975; Langer & Pooley, 1973; Langer et al., 1972a,b; Pooley, 1975). The latter technique allows the collection of morphological, structural and chemical data that allow unique identification of all single sub-microscopic fibres that occur in the environment.

4. Comments on Data Reported and Evaluation

All commercial forms of asbestos tested are carcinogenic in mice, rats, hamsters, and rabbits. In mice, mesotheliomas were induced following intraperitoneal injection of asbestos fibres. In rats, various types of asbestos produced lung carcinomas and mesotheliomas following their inhalation and mesotheliomas and sarcomas following their intrapleural or intraperitoneal injection. The oral administration of asbestos filter material to rats also resulted in an increased incidence of tumours. Mesotheliomas were produced in hamsters and rabbits after intrapleural injection of a number of types of asbestos fibre.

The size and shape of the fibres influence the incidence of tumours; fibres less and 0.5 μm in diameter are more active in producing tumours. Glass fibres and nemalite of a similar size can also produce mesotheliomas following their intrapleural or intraperitoneal injection in rats.

In humans, occupational exposure to chrysotile, amosite, anthophyllite and mixed fibres containing crocidolite has resulted in a high incidence of lung cancer; a predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also cause an increased incidence of lung cancer. Many pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite, and chrysotile. An excess risk of gastrointestinal tract cancers has been demonstrated in groups exposed occupationally to amosite, chrysotile or mixed fibres containing crocidolite. An excess of cancers of the larynx was also observed in exposed workers. Mesotheliomas also occur in individuals living in the neighbourhood of asbestos factories and crocidolite mines and in household contacts of asbestos workers.

Occupational exposure to asbestos may occur during the mining of fibrous minerals, as well as of minerals embodied in rocks, which may contain asbestiform fibres as a contaminant.

Both cigarette smoking and occupational exposure to asbestos fibres independently increase lung cancer incidence, but when they are present together they act in a multiplicative fashion.

## APPENDIX A

The criteria for the evaluation of the carcinogenic risk of chemicals to man were established at a number of meetings held prior to the publication of Volume 1 of the IARC Monograph series. All volumes published since that time have followed essentially the same format and are based on the same criteria. Working Groups have been limited to the assessment of published data, on which the final evaluation in terms of carcinogenic potential is based. In order to ensure, however, that the monographs will continue to provide accurate and extensive evaluations in changing circumstances, it has been decided to convene a Working Group to review the criteria used up until now.

The present Working Group, convened to evaluate asbestos, felt, however, that in view of the importance of this substance, this monograph should also present a quantitative evaluation of the future scope of the problem in terms of society as a whole. Such forecasts are dependent on several variables which cannot be predicted with certainty.

Without implying disagreement with the views of the Working Group, the Director of IARC has requested that this section appear as an Appendix to the main text of the monograph.

### SCOPE OF THE PROBLEM RELATED TO ASBESTOS EXPOSURE

In the first half century of modern commercial use of asbestos (1878-1927), there were only sporadic reports of associated health risks, and these were concerned with pneumoconiosis, in particular asbestosis (Cook 1927). During those years the use of this versatile material expanded greatly, with few precautions against exposure. In spite of the fact that the hazards from exposure to asbestos dust had been clearly defined by Merewether & Price (1930) in the UK, by Dreessen et al. (1938) in the US and by Nordmann (1938) in Germany, insufficient action was subsequently taken. By the time the cancer potential had been recognized and defined (1935-1960), asbestos has permeated much of modern industry, and, indeed, modern society, with thousands of products being manufactured and utilized throughout the world, in circumstances that we now understand were inadequate for the control of occupational disease, including cancer. As a result, we are now faced with a double dilemma, or how to deal with the consequences of previous inattention and error, in terms of human disease, and of how to avoid further exposure that could produce disease in the future.

The results of failures in the past spur efforts for control [See, e.g., Senior Medical Inspector's Advisory Panel (1968)]. In many studies of groups of asbestos workers, for example, approximately 20% of all deaths are the result of lung cancer, three-quarters of which are attributable to their work with asbestos (Selikoff, 1976b). Among other groups, pleural and peritoneal mesotheliomas have become common; estimates for certain groups suggest that as many as 7-11% may die of these diseases (Newhouse & Berry, 1976), which otherwise occur only rarely. Excess incidences of gastro-intestinal, laryngeal and orophanyngeal cancer will claim further lives. There are few accurate estimates of the numbers of persons at risk from exposure to asbestos in the various countries of the world. Attempts to do so have been made in the US (Wagoner, 1976), and it is sobering to realize that there are now in the US approximately 1 million men and women who work regularly in manufacturing asbestos products or who were so employed in the past. Should the foregoing estimates hold for them as well, some 200 thousand deaths from mesotheliomas will occur (See also Newhouse & Berry, 1976). However, to the extent that we fail to control further exposures, these will be underestimates of the occupational cancer incidence.

Another factor that could lead to their being underestimates is that such figures may not include cancers that result from the mining and milling of asbestos or from indirect occupational exposures (as in the shipyard and construction industries), from a number of specific uses of asbestos materials (as in brake repair and brake maintenance work), or from para-occupational exposure or uncontrollable consumer use of asbestos materials; nor do they include cancers that will result from household contact or neighbourhood exposures. Indeed, no population exposed to the industrial use of asbestos has escaped this hazard. It is also likely that every country in the world has experienced this public health problem.

The general population may also be exposed to asbestos fibres in air, beverages, drinking-water, food and pharmaceutical and dental preparations and by consumer use of asbestos-containing products. The presence of asbestos and asbestiform minerals from natural sources in the environment, other than mines or quarries, has only recently shown itself to be a further potential problem.

At present, it is not possible to assess whether there is a level of exposure in humans below which an increased risk of cancer would not occur.

# AURAMINE

## 1. Chemical and Physical Data

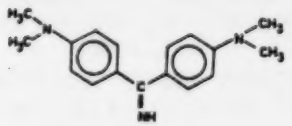
### 1.1 Synonyms and trade names

Chem. Abstr. No.: 492808; Name: C.I, solvent yellow 34

Aniline, 4,4'-(imidocarbonyl)-bis(N,N'-dimethyl-; 4,4'-Imidocarbonyl-bis (N,N'-dimethyl)aniline; 4,4'-Dimethylamino-benzophenonimide; bis(p-Dimethyl-aminophenyl) methyleneimine; Tetramethyl-p-diamino-imido-benzophenone; Tetramethyldiamino-diphenylacetimine; Apyonine auramine base; Auramine N base; Auramine O Base; Auramine SS; Auramine OO, Brilliant oil yellow; C.I. basic yellow 2 (free base); Fat yellow A; Yellow pyoctanine; Glauramine

### 1.2 Chemical formula and molecular weight

As Base:



$C_{17}H_{21}N_3$

Mol. wt: 267.36

As hydrochloride: $C_{17}H_{22}ClN_3.H_2O$

### 1.3 Chemical and physical properties of the pure substance

(a) Description

Base: Yellow leaves

Hydrochloride: Yellow needles

(b) Melting-point: Base: 136°C (rapid heating)

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* Considered by the Working Group in Geneva, December 1971.

(c) Solubility

Base: Insoluble in water; soluble in ethyl ether; very soluble in ethanol

Hydrochloride: Soluble in water, ethyl ether and glycerol; very soluble in ethanol and chloroform

(d) Chemical reactivity: Decomposes at temperature above 70°C; is a weak base that forms salts with HCl, $H_2SO_4$, etc.

(e) Technical products and impurities: Auramine is manufactured industrially from dimethylaniline and formaldehyde, which react to form Michler's base (tetramethyldiaminodiphenylmethane). This base is subsequently converted to auramine by heating it with sulfu and ammonium chloride in the presence of ammonia.

2. Production, Use, Occurrence and Analysis

(a) Use

The free base of auramine is used to prepare Solvent Yellow 34, a solvent-soluble yellow dye.

It has been reported in the United Kingdom that auramine has come into prominence as a powerful antiseptic for use in nose and ear surgery. Also, in the United Kingdom, a specially purified auramine, sold under the name of Glauramine, is used as an antiseptic in the treatment of gonorrhoea.[1]

Auramine and its hydrochloride are used in large quantities in the colouring of paper and cardboard and, to a lesser extent, of some textiles and leather. In the first-mentioned case, they are added during the processing of the raw material prior to manufacture. Auramine has been used in some countries as a food dye. It is also used as a smoke dye (Tatyrek, 1965).

(b) Analytical Methods

Guidelines for the analysis of aromatic amines have been given (UICC, 1970). A method for the determination of auramine in certain smoke mixtures has been described by Ripley & Need (1961).

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[1] Data from Chemical Information Services, Stanford Research Institute.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal Data

Auramine is a carcinogenic in the mouse and rat. Given orally, it has produced liver tumours in these two species. No tumours were obtained in the only experiment in the dog and in the rabbit. The purity of the auramine used is these experiments is not known.

### 4.2 Human Data

One epidemiological study indicates that the open manufacture of auramine presents an occupational bladder cancer risk.

# BENZENE

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. No.: 71-43-2

Benzin**; benzine**; benzol; benzole; benzolene; bicarburet of hydrogen; carbon oil; coal naphtha; cyclohexatriene; motor benzol; phene, phenyl hydride; mineral naphtha; pyrobenzol; pyrobenzole

### 1.2 Chemical formula and molecular weight:

$C_6H_6$ Mol. wt: 78.1

### 1.3 Chemical and physical properties of the pure substance

(a) Description: Clear, colourless, highly flammable liquid

(b) Boiling-point: 80.1°C

(c) Melting-point: 5.5°C

(d) Density: $d_4^{15}$ 0.8787

(e) Refractive index: $n_D^{29}$ 1.5016

(f) Volatility: The vapour pressure is 74.6 mm Hg at 20°C.

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* Considered by the Working Group in Lyon, June 1974

** These two names are no longer used for benzene. They have been used for many years to describe a low-boiling petroleum fraction predominantly containing aliphatic hydrocarbons (Ayers & Muder, 1964).

(g) Solubility: Slightly soluble in water (0.8 part by weight in 1000 parts of water at 20°C); miscible with acetone, alcohol, carbon disulphide, carbon tetrachloride, chloroform, ether, glacial acetic acid and oils

## 1.4 Technical products and impurities

Commercial crystallizable benzene contains 99-100% benzene and has a boiling-point of 80-81°C. The typical specifications for commercial grades of benzene are: nitration grade - a distillation range not greater than 1°C and including the temperature 80.1°C; industrial grade - a distillation range not greater than 2°C and including the temperature 80.1°C; refined benzene - 0.0032 mg/l (1 ppm) maximum of thiophene, 0.15% maximum of nonaromatics and a distillation range not greater than 1°C and including the temperature 80.1°C. None of the grades must contain acidity (American Society for Testing Materials, 1968).

## 2. Production, Use, Occurrence and Analysis

A review on benzene has been published (Ayers & Muder, 1964).

## 2.1 Production and use[1]

Benzene was first isolated by Faraday in 1825 from a liquid condensed by compressing oil gas. Synthesis, by the polymerization of acetylene, was first carried out in 1866 by Berthelot. Benzene has been produced commercially from coal since 1849 and from petroleum since 1941. Since 1959 the major U.S. source of benzene has been petroleum (Ayers & Muder, 1964).

Various petroleum refinery techniques are used for the production of benzene: catalytic reforming (approximately 67% of the total US production is now made *via* this route), hydrodealkylation, pyrolysis of gasolene, toluene disproportionation and dealkylation of higher alkyl aromatics. High-temperature carbonization of coal yields coal-tar, which contains benzene; however, due to increasing dependence on petrochemical derivatives, the amount of benzene derived from coal sources has become only a small part of total production and was estimated to be only 12% of US production in 1971.

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1 Data from Chemical Information Services, Stanford Research Institute, USA.

In the US, Puerto Rico and the Virgin Islands there are 31 producers of petroleum-based benzene, and there are 9 in the US who manufacture coal-derived benzene.

US benzene production has shown steady growth from 459 million kg in 1940 (US Tariff Commission, 1941) to 3,928 million kg in 1972 (US Tariff Commission, 1974a). Preliminary information indicates that 1973 production was 4,649 million kg (US Tariff Commission, 1974b).

In 1972, the US exported 96.8 million kg benzene (US Department of Commerce, 1972a) and imported 317.2 million kg (US Department of Commerce, 1972b). Since 1967 there has been a decline in exports of benzene, whereas imports have grown steadily during this same period.

Benzene is produced for chemical purposes in the following Western European countries (the number of producers followed by the total production in 1972 in million kg are given in parentheses): Austria (1; 15), Belgium (3; 40), the Federal Republic of Germany (9; 827), France (7; 383), Italy (7; 503), The Netherlands (2; 554), Spain (4; 118), and the United Kingdom (8; 556) (EEC, 1973; Sindicato Industrias Quimicas, 1972).

In Japan, benzene is produced by 23 companies whose primary methods of production are by extraction from reformed or cracked naphtha and by dealkylation of toluene. During the period 1970-1972, production grew at the rate of 14% per year, reaching 1,575 million kg in 1972. During the same period, imports grew from approximately 1.8 million kg in 1970 to nearly 18 million kg in 1972. Exports in 1972 were 129.8 million kg; 90% of this went to the US.

Although its major use in the US for many years was in blends with gasolene, this usage stopped almost entirely after World War II. An estimated 1971 US consumption pattern of benzene as a chemical intermediate and for other non-fuel uses follows: in ethylbenzene, 44.2%; in phenol, 19.2%; in cyclohexane, 15.6%; in maleic anhydride, 3.9%; in detergent alkylate, 3.9%; in aniline, 3.5%; in dichlorobenzenes, 1.1%; in DDT, 0.5%; and in miscellaneous other non-fuel uses, 8.1%. The most significant increases in the use of benzene in the years since 1945 have been in the manufacture of cyclohexane (only 4.1% of total consumption in 1945) and ethylbenzene (only 22.8% in 1945).

Ethylbenzene is used in the production of styrene, which is used for the manufacture of a wide variety of elastomers and plastics. Phenol is used mainly as an intermediate for the synthesis of phenol-formaldehyde, phenol-furfural and other

phenol-derived resins used primarily in the construction industry as adhesives and laminating resins. Cyclohexane is an imporatant raw material for the manufacture of caprolactam for nylon 6 and of adipic acid and hexamethylenediamine, which are used chiefly in the synthesis of nylon 66.

It has been reported that benzene was formerly used in human medicine for the treatment of leukaemia, polycythaemia vera and malignant lymphoma; and it has been said to be useful in veterinary medicine to destroy screw-worm larvae in wounds (Merck & Co, 1968). Benzene has been used as a solvent in the manufacture of paints and, since it is also a solvent for rubber, in rubber cements (Ayers & Muder 1964).

The following benzene consumption pattern in Western Europe in 1970 has been estimated: in styrene, 40%; in phenol (via cumene), 20%; in cyclohexane, 23%; and in miscellaneous uses, 17% (Waddams, 1973).

In Japan, the major uses for benzene are in the manufacture of: styrene monomer (via ethylbenzene), 48%; cyclohexane, 26%; phenol, 16%; alkylbenzene, 4%; and maleic anhydride, 2%; miscellaneous uses account for 2%.

## 2.2 Occurrence

Benzene occurs in straight-run petroleum distillates and in coal-tar distillates, e.g., light oil from coke-oven gas (Ayers & Muder, 1964). It has been reported that all motor gasolenes (petrols) contain small quantities of benzene, usually less than 5%; although special motor fuels can contain up to 30% benzene. Analysis of the ambient air in gasoline filling stations and at bulk tanker-loading installations gave mean benzene concentrations of 0.001-0.008 mg/l (0.3-2.4 ppm) at 9 gasoline filling stations and 0.001-0.02 mg/l (0.3-6.7 ppm) during normal operations at bulk filling facilities handling normal motor gasolene. Some variation occurred depending on weather conditions; in damp misty weather with no wind, concentrations did not exceed 0.06 mg/l (19.5 ppm) (Parkinson, 1971).

Using a gas chromatographic method, Lonneman et al. (1968) detected an average concentration of benzene of 0.00005 mg/l (0.015 ppm) by volume in Los Angeles air. The highest measured concentration was 0.0002 mg/l (0.057 ppm).

The US Occupational Safety and Health Administration health standards for air contaminants require that an employee's exposure to benzene does not exceed an eight-hour time-weighted

average of 0.032 mg/l (10 ppm) in the workplace air in any eight-hour workshift for a forty-hour work week. In addition, the exposure may not exceed a ceiling concentration of 0.08 mg/l (25 ppm) except for a time period of 10 minutes maximum in which the concentration may be as high as 0.16 mg/l (50 ppm) (US Code of Federal Regulations, 1974). It is reported that a level of approximately 0.08 mg/l (25 ppm) is generally considered to be the maximum admissible in other countries, but the maximum concentration permitted in the USSR is approximately 0.02 mg/l (6 ppm) (ILO, 1968).

## 2.3 Analysis

An indicator-tube method based on the colour reaction between benzene vapours and silica gel treated with a 5% solution of cerium sulphate in fuming sulphuric acid has been described. The method is sensitive to 0.005 mg/l (1.5 ppm), with an accuracy of ±15% for low concentrations of benzene and of ± 5% for high concentrations (Koljkowsky, 1969).

Maffet et al. (1956) described a quick method for the determination of pure benzene in air [less than 0.1 mg/l (35 ppm)]. The benzene is collected in a sampling tube containing silica gel (collection rate, 1.2-1.5 l/min), and the amount retained is determined spectrophotometrically by comparing the absorbance in iso-octane at 254.5 nm with a standard calibration curve. Collection of benzene in air and on various gels and its determination by gas chromotography have been described by Sherwood & Carter (1970). A similar procedure for breath samples is also described, together with a method for determination of the concentration of phenol in the urine of workers exposed to benzene. By such a method, a breath concentration of 0.14 ppm (0.0004 mg/l) benzene has been determined (Sherwood, 1972). Colorimetric and gas chromatographic methods for the determination of phenol in the urine of workers exposed to benzene have been described by Van Haaften & Sie (1965)

The qualitative detection of specific compounds in industrial atmospheres using activated charcoal columns, gas chromatography and mass spectrometry for the collection, separation, analysis and qualitative identificatin of compounds has been described. The limit of identification of benzene in airborne mixtures of organic vapours in these studies was 20 ppm (Cooper et al., 1971).

Gas chromatographic determination of traces of benzene in industrial solvents (Hoffelt & Bourdon, 1969) and in automobile exhaust gases (Ishii & Musha, 1971) have also been described.

Other analytical methods including one recommended by IUPAC are included in a review on benzene (ILO, 1968).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal Data

Benzene has been tested only in mice by subcutaneous injection and skin application. The data reported do not permit the conclusion that carcinogenic activity has been demonstrated.

### 4.2 Human Data

It is established that exposure to commercial benzene or benzene-containing mixtures may result in damage to the haematopoietic system. A relationship between such exposure and the development of leukaemia is suggested by many case reports, and this suggestion is strengthened by a case-control study from Japan.

# Benzidine

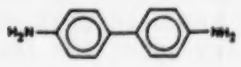
## 1. Chemical and Physical Data

### 1.1 Synonyms and trade Names

Chem. Abstr. No.: 92875

Biphenyl, 4,4'-diamino-; 4,4'-Biphenyldiamine; C.I. azoic diazo component 112; 4,4'-Diaminobiphenyl; 4,4'-Diphenylenediamine; Fast Corinth base B; p-Diaminodiphenyl; 4,4'-Diaminodiphenyl

### 1.2 Chemical formula and molecular weight



$C_{12}H_{12}N_2$ Mol. wt: 184.23

### 1.3 Chemical and physical properties of the pure substance

(a) Description: A colourless, crystalline compound that darkens on oxidation

(b) Melting-point: 128°C (rapid heating)

(c) Solubility and volatility: Slightly soluble in cold water; more soluble in hot water and readily soluble in less polar solvents such as diethyl ether and ethanol; can be sublimed.

(d) Chemical reactivity: A weak base that forms insoluble salts with $H_2SO_4$; can be diazotized and oxidized, and its amino groups can be acetylated and alkylated.

(e) Technical products and impurities: Semidines and o,o- and o,p-benzidines are products of its manufacture from hydrazobenzene.

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* Considered by the Working Group in Geneva, December 1971.

[1] Data from Chemical Information Services, Stanford Research Institute.

## 2. Production, Use, Occurrence and Analysis

### 2.1 Use and occurrence

#### (a) Use

In the USA, the production of benzidine amounts to many million pounds annually. According to the Colour Index, more than 250 dyes are derived from benzidine.[1]

Benzidine and its salts are used in the manufacture of dyestuffs based on the coupling of tetrazotized benzidine with phenols and amines. It has been, and still may be to come extent, used in the rubber industry as a hardener. It has been used for specialized processes such as the manufacture of plastic film, but not after 1956, at least in one country. It is used clinically for the detection of blood. It is used for the detection of $H_2O_2$ in milk. It reacts with ink erasers to give coloured products and therefore has been used in security printing. It is also used as a laboratory agent for the detection of HCN and sulfate, for the quantitative determination of nicotine and as a spray reagent for sugars.

#### (b) Analytical methods

Methods for the determination of benzidine in the air, plant deposits, and clothing have been described by Butt & Strafford (1956).

#### (c) Occurrence

It has been suggested that benzidine may be produced from 1,2-diphenyl-hydrazine (hydrazobenzene) by acidity in the stomach.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal Data

Benzidine is carcinogenic in the mouse, rat and hamster, and possibly the dog. Given orally, it has produced bladder carcinoma in the dog after a long latent period and liver tumours in the rat and hamster.

## 4.2 Human Data

The epidemiological studies showed that occupational exposure to commercial benzidine alone was strongly associated with bladder cancer. In the same studies, exposure to 2-naphthylamine alone was similarly associated with bladder cancer. A number of case reports from several countries support the relationship between this neoplasm and occupational exposure to benzidine.

## N,N-Bis(2-Chloroethyl)-2-Napthylamine*

### 1. Chemical and Physical Data

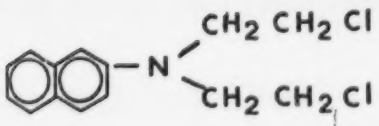
#### 1.1 Synonyms and trade names

Chem. Abstr. No.: 49-40-31

CB 1048; chlornaftina; chlornaphazin; chlornaphazine; chlornaphthin; chloronaftina; chloronaphthine; dichloroethyl beta-naphthylamine; di(2-chloroethyl)-beta-naphthylamine; naphthylamine mustard; beta-naphthyl-bis(beta-chloroethyl)amine; beta-napthyl-di-(2-chloroethyl)amine

Erysan; R48

#### 1.2 Chemical formula and molecular weight



$C_{14}H_{15}Cl_2N$ Mol. wt: 268.2

#### 1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless plates

(b) Boiling-point: 210°C

(c) Melting-point: 54-56°C

(d) Solubility: Very sparingly soluble in water and glycerol; more soluble in petroleum ether, ethanol, olive oil, ether, acetone and benzene (in ascending order)

(e) Chemical reactivity: A nitrogen mustard; it reacts with nucleophiles. A detailed study of the hydrolysis in aqueous acetone has been made (Ross, 1949).

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* Considered by the Working Group in Lyon, June 1973.

## 1.4 Technical products and impurities

No information is available to the Working Group.

## 2. Production, Use, Occurrence and Analysis

### (a) Production and use[1]

No evidence was found that it has ever been produced commercially or found commercial usage in the United States. However, this compound has been used in a number of countries as a chemotherapeutic agent for the treatment of leukaemia and of Hodgkin's disease (Videbaek, 1964) as well as for the control of polycythaemia vera (Thiede et al., 1964). It has reportedly been withdrawn from use in Denmark because of detected instances of cancer of the bladder following its administration. Although it still appears in some drug directories, N,N-Bis(2-chloroethyl)-2-napthylamine probably does not have wide therapeutic usage.

### (b) Occurrence

N,N-Bis(2-chloroethyl)-2-naphthylamine has not been reported to occur as such in nature.

### (c) Analysis

No methods specific for the analysis of chlornaphazine are known to the Working Group. General methods for the detection of alkylating agents are available (Preussmann et al., 1969; Sawicki & Sawicki, 1969).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

N,N-Bis(2-chloroethyl)-2-naphthylamine is carcinogenic to the mouse lung by the intraperitoneal route and has a local carcinogenic effect in rats following subcutaneous injection.

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[1] Data from Chemical Information Services, Stanford Research Institute, USA.

## 4.2 Human data

This drug has been administered to man with $^{32}P$ sodium phosphate for the treatment of polycythaemia and of neoplasias of the haemopoietic system in doses of up to 400 mg/day. Follow-up studies have shown that under these conditions, the drug is carcinogenic, producing bladder tumours after administration of total doses as low as 4 g.

## Bis(chloromethyl)ether*

### 1. Chemical and Physical Data

#### 1.1 Synonyms and trade names

Chem. Abstr. No.: 432-88-1

BCME: Chloromethyl ether[1]; chloro(chloromethoxy)methane; dichloromethyl ether; symmetrical-dichloro-dimethyl ether; symmetrical dichloromethyl ether; dimethyl-1,1'-dichloroether

#### 1.2 Chemical formula and molecular weight

$ClCh_2OCH_2Cl$ $C_2H_4Cl_2O$ Mol wt: 115.0

#### 1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless liquid

(b) Boiling-point: 104°C at 760 mm

(c) Density: $d_4^{15}$ 1.328

(d) Refractive index: $n_D^{20}$ 1.435

(e) Solubility: Miscible with ethanol, ether and many other organic solvents

(f) Volatility: Highly volatile

(g) Stability: Decomposes in the presence of water into hydrochloric acid and formaldehyde. About 70% of bis-(chloromethyl)ether (BCME) is hydrolyzed in heavy water ($D_2O$) in two minutes and 80% after 18 hours, suggesting the attainment of an equilibrium between bis(chloro-methyl)ether and its hydrolysis products (Van Duuren et al., 1969). It was recently reported that BCME at 10 and 100 ppm is stable in air with 70% relative humidity for at least 18 hours (Collier, 1972).

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* Considered by the Working Group in Lyon, June 1973.

1 This name is sometimes used in error for chloromethyl methyl ether.

## 1.4 Technical products and impurities

It has been reported that one grade of "commercial" BCME was >99% pure and contained a trace of carbonyl-containing impurity (Van Duuren et al., 1968).

## 2. Production, Use, Occurrence and Analysis

### (a) Production and use[1]

BCME can be produced by saturating a solution of paraformaldehyde in cold sulphuric acid with hydrogen chloride.

Although BCME may be produced in the United States as a chemical intermediate, no evidence was found that it is produced on a commercial scale for sale to others. Several companies which sell laboratory chemicals offer it for sale, but apparently these companies merely serve as repackagers or distributors (the source of the chemical they repackage is not known). In 1967, one manufacturer of laboratory and experimental chemicals in the Federal Republic of Germany was reported to be offering BCME for sale. No information is available on the production of BCME in other countries, but it seems likely that it is produced at least as a chemical intermediate.

Alpha-halo ethers such as BCME were reported to have proved useful in the laboratory synthesis of other organic chemicals, and 30 or 40 patents have appeared since 1940 describing the preparation of various textile aids from chloromethyl ether with amides, amines, alcohols and other reagents (Summers, 1955). Such textile aids are not necessarily prepared from previously isolated halomethyl ethers.

In 1968, it was reported that at least 28 patents had appeared in Chemical Abstracts during the last decade concerning the synthesis and applications of chloromethyl methyl ether and bis(chloromethyl)ether. In spite of this apparent interest in BCME, sales in the US appear to have been limited to laboratory quantities (Van Duuren et al., 1968).

The largest potential source of human exposure to BCME appears to be in the use of a chloromethylating reaction mixture made from methanol, formaldehyde and hydrochloric acid. BCME

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1 Data from Chemical Information Services, Stanford Research Institute, USA.

can be a major component of these reaction mixtures, which are used without isolation of the individual products for chloromethylating a variety of organic compounds. The chloromethylated products are primarily chemical intermediates which are often subsequently converted to aminated compounds by reaction with organic amines. Probably the largest single usage of chloromethylation is in the preparation of anion exchange resins. A modified polystyrene resin is chloromethylated and then treated with a tertiary amine or with a poly amine. These resins have been produced in the US, and their production in 1966 in the Federal Republic of Germany, in the German Democratic Republic, France, Italy, Japan, The Netherlands, United Kingdom and USSR has also been reported (Abrams & Benezra, 1967). However, no data are available on the quantities of resins produced.

Other chloromethylated compounds of commercial significance include chloromethyl diphenyl oxide, 1-chloromethylnaphthalene, di(chloromethyl) diphenyl oxide, di(chloromethyl)toluene and dodecylbenzyl chloride. No data are available on the total production of these chemicals, since they are largely used captively.

(b) Occurrence

BCME does not occur as such in nature. Because it hydrolyzes in water, it would not be expected to remain as such for protracted periods in waste streams from plants where it is produced or used. However, in view of its reported stability in moist air, it might be present in exhaust gases from such plants (Collier, 1972).

BCME is listed together with 13 other chemicals in the US Federal Register (US Government, 1973) as being subject to an Emergency Temporary Standard on certain carcinogens under an order made by the Occupational Safety and Health Administration, Department of Labor on 26 April, 1973.

(c) Analysis

A high-resolution mass spectral procedure which can measure BCME at the 0.1 ppb level in air containing other organic compounds has been developed (Collier, 1972). Gas chromatography can also be used. Several methods for the detection of alkylating agents have been reported (Preussmann et al., 1969; Sawicki & Sawicki, 1969).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Bis(chloromethyl)ether (BCME) is carcinogenic to mice following inhalation, skin application and subcutaneous administration. In newborn mice, it is carcinogenic after a single subcutaneous exposure. In the rat it is carcinogenic by inhalation and subcutaneous administration.

### 4.2 Human Data

A high incidence of predominantly oat-celled carcinoma in a small population of laboratory workers exposed to BCME strongly suggests that exposure to this compound constitutes a serious human lung cancer hazard.

There is also epidemiological evidence to suggest that exposure to BCME may consitute a lung cancer risk amongst workers exposed to it as a contaminant in the manufacture of the related CMME (see separate monograph on CMME).

## Cadmium and Inorganic Cadmium Compounds*

### 1. Chemical and Physical Data

#### 1.1 Identity

| Chemical Name | Formula | Chem. Abstr. No. | Synonyms |
|---|---|---|---|
| Cadmium | Cd | 7440-43-9 | C.I. No. 77180[1] |
| Cadmium carbonate | $CdCO_3$ | 513-78-0 | Carbonic acid, Cadmium salt (1:1)<br>Otavite |
| Cadmium chloride | $CdCl_2$ | 10108-64-2 | Cadmium dichloride |
| Cadmium oxide | CdO | 1306-19-0 | -- |
| Cadmium sulphate | $CdSO_4$ | 10124-36-4 | Sulphuric acid, cadmium salt (1:1) |
| Cadmium sulphide | CdS | 1306-23-6 | Aurora yellow[2]<br>C.I. No. 77199[1]<br>C.I. No. pigment orange 20[1]<br>C.I. No. pigment yellow 37[1]<br>Greenockite |

* Considered by the working group in Lyon, December 1972.

1 Colour Index number.

2 Does not include pigments where cadmium is part of the name, and trade-name pigments.

## 1.2 Solubility

The cadmium compounds considered in this monograph are insoluble in water, except for the chloride and sulphate. The chloride is also soluble in alchohols. The solubility of the metal in tissues and body fluids has been discussed by Weinzierl & Webb (1972).

## 1.3 Stability

The cadmium compounds considered are stable.

## 2. Production, Use, Occurrence and Analysis

### (a) Use

Cadmium: The world production of cadmium was around 35 million pounds in 1970. The principal sources of cadmium are the sintering of flue dusts and the roasting of zinc ores. Some cadmium metal is also recovered as a by-product of the purification by distillation of slag zinc.

Standard grades of commercial cadmium are usually 99.9% pure. Cadmium sponge is also available for the manufacture of cadmium chemicals, and it typically ranges from 86% to 92% cadmium, with a sizable proportion of the impurity being oxygen (due to the presence of cadmium oxide).

The estimated US consumption patterns (expressed in millions of pounds) for cadmium in all forms (i.e., metal, alloys and compounds) for 1968 and 1971 are as follows: electroplating 7.0, 4.50; plastics stabilizers 2.5, 2.34; pigments (including phosphors) 2.0,. 1.26; metal alloys 0.5, -; batteries 0.4, -; others 0.9, -; metal alloys, batteries and others 1.8, 0.90; total 13.3, 9.0.

Cadmium electroplated on metals (primarily steel) is superior to zinc in providing resistance to corrosion.

Nearly all the electroplating is accomplished in baths formulated from cadmium metal and cadmium oxide dissolved in a sodium cyanide solution. These baths consume only an estimated 20% of the total amount of cadmium used in electroplating. Cadmium metal anodes supply the remaining 80%.

The most important applications of electroplating are in automotive and aircraft parts, electronic parts, marine equipment and industrial machinery.

The next largest end use for cadmium is in the production of organo-cadmium compounds which serve as stabilizers for plastics. The most common stabilizers are mixtures of cadmium and barium salts of long-chain fatty acids.

Another use of cadmium is in the preparation of cadmium sulphides, cadmium selenides and mixtures containing these salts for use as pigments (including phosphors). The phosphors require very pure starting materials and cadmium oxide is preferred as the cadmium source.

Cadmium-containing alloys are used for bearings where the high speeds and temperatures are excessive for tin or lead alloys. Such bearing alloys contain about 99% cadmium in combination with nickel, silver and/or copper. Cadmium alloys used for soldering aluminum contain 10-95% cadmium, with zinc or silver as the other elements. Low-melting alloys of cadmium contain 8-40% cadmium in combination with bismuth, indium, tin and/or lead, and these alloys are used in a variety of applications (e.g., fire-protection fusible links, fusible cores for foundry moulds, holding irregular parts for machining, bending pipes and thin sections, soldering and sealing).

Cadmium is used as the negative electrode in nickel-cadmium storage batteries used in industrial equipment, motor vehicles and many rechargeable household appliances.

Other uses of cadmium that consume minor quantities include alloys for neutron shields and control rods for nuclear reactors.

Cadmium carbonate: Cadmium carbonate can be prepared by absorption of carbon dioxide in cadmium hydroxide solution, and this is believed to be the main commercial process.

Cadmium carbonate is available in a commercial grade having a purity of about 98%. Lead, zinc and iron are present as impurities. Higher purity grades are available for special applications.

The major application is believed to be in fungicides. Cadmium carbonate is used as a lawn and turf fungicide in concentrations of 3.0 and 5.3% as a wettable powder in combination with organic fungicides. The next most significant use is in the preparation of high purity specialty chemicals such as phosphors.

Cadmium chloride: Cadmium chloride is made by dissolving cadmium metal in hydrochloric acid and evaporating to dryness in a stream of hydrogen chloride gas, or by dissolving cadmium

oxide or carbonate in hydrochloric acid. The commercial chemical is a mixture of hydrates that approximates to the dihydrate ($CdCl_2.2H_2O$).

The commercial grade of cadmium chloride available in the US typically contains about 51% cadmium and 0.005% each of iron and copper as impurities. There are higher purity grades available for specialised applications such as photographic chemicals and phosphors.

It is believed that pesticides are the largest single use of the commercial grade, and that photographic materials (increasingly) and phosphors are the largest users of higher purity cadmium chloride.

Cadmium chloride is used in no-pasture turf fungicides (cadmium nitrate and cadmium carbonate are used alternatively).

Minor uses for the chloride include its applications in dyeing and calico printing of textiles, the manufacture of thermionic emission coatings for electronic vacuum tubes, as a lubricant ingredient, and in the manufacture of special mirrors.

Cadmium oxide: Cadmium oxide is made commercially by distilling cadmium metal from a graphite retort and allowing the vapour to react with air. The commercial grade of cadmium oxide which is available in the US has a reported purity of 99.7%, with lead and thallium as detectable impurities.

It is generally agreed that electroplating is by far the largest market for cadmium oxide. Total consumption of cadmium in electroplating in the US was estimated at 7 million pounds for 1968 and 4.5 million pounds for 1971. Other important applications are in the manufacture of cadmium electrodes for alkaline storage batteries and in the synthesis of other cadmium salts.

Cadmium sulfate: Cadmium sulfate is made commercially as both the anhydrous ($CdSO_4$) and the hydrated salt ($3CdSO_4.8H_2O$). The usual route for the commercial production of these materials involves dissolving the metal, oxide, carbonate or sulphide in sulphuric acid with subsequent cooling or evaporation to precipitate the salt. Cadmium sulphate is also made as an intermediate in the recovery of cadmium from zinc ore.

Commercial grade cadmium sulphate reportedly contains about 49.5% cadmium (the theoretical cadmium content of $CdSO_4$ is 53.5%).

The principal uses of cadmium sulphate are as an intermediate for plastic stabilizers and in pigments. These uses are estimated to have consumed 3.6 million pounds of cadmium in 1971 in the US.

Cadmium salts of long-chain fatty acids are used as stabilizers for plastics (especially polyvinyl chloride). Cadmium sulphate is used in the manufacture of cadmium sulphide pigments (including phosphors), of cadmium lithopone pigments, and of cadmium sulphoselenide pigments. The use of cadmium sulphate in medicinal preparations has been discontinued because of its toxicity.

Cadmium sulphide: Cadmium sulphide is produced commercially by the reaction of hydrogen sulphide gas with a cadmium salt (mostly cadmium sulphate). It is used mainly in pigments and phosphors that range in colour from yellow to deep maroon.

Because cadmium sulphide and cadmium sulphide-containing materials are used typically for their physical properties rather than for their chemical compositions, the usual measures of product grades are seldom used. Although the commercial grade of cadmium sulphide not otherwise identified as a pigment or a phosphor has a typical content of 98.8% cadmium sulphide and 0.7% cadmium sulphate, most products are much more complex. Thus, cadmium yellow pigments are cadmium sulphide-zinc sulphide mixtures; cadmium lithopone pigments are coprecipitates of cadmium sulphide and barium sulphate; cadmium sulphoselenides are varied mixtures of cadmium sulphide, cadmium selenide and selenium sulphide; and the so-called mercadium pigments contain mercuric sulphide in combination with cadmium sulphide. The cadmium sulphide used in phosphors is usually part of a mixture with zinc sulphide which contains trace amounts of activators such as silver, copper or nickel.

Almost all of the cadmium sulphide produced in the US is used in pigments (including phosphors). These pigments find their principal applications where heat stability (e.g., in coloured vulcanized rubber and some epoxy resins), alkali resistance (printing inks) and resistance to hydrogen sulphide blackening (paints and artists' colours) are needed. Other materials for which cadmium sulphide pigments have been found useful include glass, ceramics, textiles and paper.

Cadmium sulphide finds its principal phosphor application in cathode ray tube screens. Minor quantities of cadmium sulphide are used in a variety of applications that benefit from the low energy levels required to obtain visible light from this chemical. Phosphorescent tapes and markers, watch and instrument dials, interior decorations, and theatrical black magic are

popular uses. X-ray fluorescent screens and body temperature gradient detectors are medical uses.

Cadmium sulphide is the active ingredient in a shampoo designed for use in the treatment of seborrheic dermatitis of the scalp.

(b) Analytical Methods

Trace analysis of cadmium may be performed by a number of instrumental methods. The preferred routine technique is atomic absorption spectroscopy, but colorimetry is frequently used due to lower instrumentation cost. A brief survey of techniques is given by Friberg et al. (1971).

(c) Occurrence

Cadmium

Natural Environment: Cadmium is a relatively rare element in the earth's crust. Greenockite (CdS) is its most common mineral, and in weathered ores it can be found as otavite ($CdCO_3$). In both forms it is associated with zinc and lead-zinc ores and is recovered as a by-product in the refining of these ores. Trace quantities of cadmium are found also in coals and oils.

Air: Cadmium can enter the air from these natural sources and from a variety of manufacturing operations that involve either cadmium itself (e.g., electroplating for corrosion protection) or zinc that contains cadmium impurity (e.g., galvanizing of steel). Cadmium can enter the atmosphere when cadmium-plated scrap steel is remelted. The production of refined cadmium metal is a potential source of cadmium in the atmosphere (from flue and furnace gases).

In the atmosphere of the working environment, cadmium concentrations of 1-3 $mg/m^3$ (Friberg, 1950) and 0.17-0.46 $mg/m^3$ (Hardy & Skinner, 1947) have been reported.

Air is not a significant source of cadmium as compared with food. In the general environment it is estimated (World Health Organization, 1972) that the daily intake would amount to 0.02 µg, and even in cities where the levels are 30 times as high this would still be small relative to the food source.

Cigarette smoke: Determinations of cadmium in cigarette tobacco point to a level of 1-2 µg per cigarette. As much as 70% of the cadmium may pass into the smoke phase (Lewis et al., 1972). For a heavy smoker this could add significantly to the daily intake. It is estimated that for each cigarette-pack-year, smokers accumulate through inhalation 0.5 mg cadmium (i.e., about 1.5 µg/day).

Water: Cadmium can enter surface waters from the natural sources described earlier and from a variety of manufacturing operations that involve either cadmium itself (e.g., electroplating for corrosion protection) or zinc that contains a cadmium impurity (e.g., galvanizing of steel). Cadmium can enter the water environment from the plating operations when spent plating solutions are discarded. The production of refined cadmium metal is a potential source of cadmium in nearby surface waters (from ore tailings and washings). Another source of cadmium appearance in surface waters is the application of phosphate fertilizers, since these have been found to contain traces of cadmium. The production of cadmium compounds is not considered a potential source of surface water contamination because of tight process controls in the manufacturing plants.

The general environment level is of the order of 1 µg/l but may be up to 10 µg/l.

Soil: Fertilized soils have been found to contain two to six times the cadmium concentration of adjacent unfertilized land.

Air, water, soil: Virtually all of the cadmium used to stabilize plastics will also enter the environment. If the plastic is incinerated after use the entry will be quite rapid.

The relative significance of some of the above applications in the US was estimated in 1968 by one source[1] and the results are tabulated:

| Sources | Quantity processed (million pounds of cadmium) | Emissions to | Estimated emissions (thousand pounds of cadmium |
|---|---|---|---|
| Primary processing sources | | | |
| Ore extraction | 4.8 | Air<br>Water, soil | 0.5<br>Not available |
| Ore concentration and metal production | 12.8 | Air | 2100 |
| Conversion of metal to products | 13.3 | Air | 33 |
| Product use | Not available | Air, water, soil | 36 |
| Recycle or disposal | -- | Air, water, soil | 2200 |
| Miscellaneous sources | | | |
| Fossil fuel combustion | 0.7 | Air | 200-700 |
| Phosphate fertilizer application | 0.05 | Water, soil | Up to 50 |
| Motor oil use | -- | Air, water, soil | 1.8 |

[1] Oak Ridge National Laboratory. Cadmium the dissipated element (ORNL-NSF-EP-21) 1972.

Food: There is little doubt that food is the main source of cadmium intake.

The presence of cadmium in a wide range of both fresh and tinned foodstuffs has been reported by Klein & Wichmann (1945). Schroeder & Balassa (1961) suggest that the main intake in the US diet was from sea foods and grain products. Vegetables were also a source (Schroeder & Balassa, 1963). In this regard,

Klein & Wichmann (1945) found a high cadmium content in tinned oysters; but this was attributed to the tinning solder which had an exceptionally high zinc content. It seems, nevertheless, that cadmium does accumulate in molluscs. A study group in Japan (Yamagata & Shigematsu, 1970) noted a major contribution of cadmium in the Japanese diet from shellfish.

Cadmium carbonate: Cadmium carbonate is found as the mineral otavite, which results from the weathering of cadmium sulphide in ores. Cadmium carbonate might appear in surface waters from the run-off of treated turf. However, it is not as soluble as cadmium chloride, which is also used as a fungicide.

Cadmium chloride: Cadmium chloride does not appear as such in nature, but it can be generated and released into the atmosphere by the incineration of polyvinyl chloride which has been stabilized with organic cadmium salts. Because of its high solubility in water, it may also appear in surface waters from the run-off of treated turf. Discharges from photographic processing may be another source.

Cadmium oxide: Cadmium oxide does not appear as such in nature, but it forms readily from the contact of cadmium vapour with air; thus it is found where cadmium is present in emissions from thermal processes such as ore roasting, pyrosmelting, steel scrap melting, incineration of wastes and burning of fossil fuels.

Cadmium sulphate: Cadmium sulphate does not appear as such in nature. However, it is found in atmospheric emissions from thermal processes involving materials containing cadmium and sulphur. Cadmium sulphate may appear in surface waters near zinc and zinc-lead ore refineries that use sulphuric acid as an ore leachant.

Cadmium sulphide: Cadmium sulphide (greenockite) is the principal mineral in which cadmium occurs, and it is found distributed in small quantities in the zinc, lead and copper ores from whose processing cadmium is a by-product. The sulphide might be found as an atmospheric contaminant in factories where it is employed; but it would probably not be found in the atmosphere of electronic component plants because there it is generally used in a slurry form. Cadmium sulphide dusts have been reported in working atmospheres. Exposure levels ranged from 18-31 mg $Cd/m^3$ of air (Princi, 1947).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Single or repeated s.c. injections of several inorganic cadmium compounds (cadmium chloride, sulphate, sulphide and oxide) result in the development of injection-site sarcomas in the rat. Local tumours were also produced in rats by i.m. injection of cadmium powder and cadmium sulphide.

Interstitial-cell tumours of the testis were found in rats and mice given s.c. injections of soluble cadmium salts (cadmium sulphate and cadmium chloride). The testicular tumours in both species were of interstitial-cell origin and were only seen following testicular atrophy. The pituitary glands of these animals showed castration changes. It is likely, therefore, that the testicular tumours developed as a result of an indirect action of cadmium on the testis. Repeated s.c. injections of cadmium sulphate in the rat failed to produce neoplastic changes in the prostate gland.

The negative results obtained when cadmium acetate was administered orally to rats and mice are not acceptable as evidence of the noncarcinogenicity of this compound since only one low dose level was used.

No conclusions could be drawn from the negative findings obtained in inhalation studies on rats with cadmium oxide and cadmium chloride fumes because of the short duration of the experiments.

### 4.2 Human Data

Two studies suggest that occupational exposure to cadmium oxide may increase the risk of prostate cancer in man, but the size of the groups examined was too small to allow definite conclusions to be drawn.

No data are available to suggest that non-occupational exposure to cadmium constitutes a carcinogenic hazard.

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[1] Personal communication from Dr. M.D. Kipling

# Cadmium and Cadmium Compounds*

## 1. Chemical and Physical Data

Cadmium and cadmium compounds were first considered by an IARC Working Group in 1972 (IARC, 1973). Since that time new data have become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

A general review of cadmium and its compounds have been published (Fulkerson et al., 1973), and a WHO Environmental Health Criteria Document is in preparation.

## 1. Chemical and Physical Data

### 1.1 Synonyms, trade names and formulae

Table I
(Chemical Abstracts names are underlined.)

| Chemical name | Chem. Abstr. Reg. Serial No. | Synonyms | Formula |
|---|---|---|---|
| Cadmium | 7440-43-9 | C.I. No. 77180 | Cd |
| Cadmium acetate | 543-90-8 | Acetic acid, cadmium salt; C.I. No. 77185 | $Cd(CH_3OOO)_2$ |
| Cadmium carbonate | 513-78-0 | Carbonic acid, cadmium salt (1:1); cadmium monocarbonate; otavi<br>Chemcarb | $CdCO_3$ |
| Cadmium chloride | 10108-64-2 | Cadmim dichloride | $CdCl_2$ |
| Cadmium fluorborate | 14486-19-2 | Borate, (1-) tetrafluorocadmium salt (2:1) | $Cd(BF_4)_2$ |

(continued)

* Considered by the Working Group, December 1975

| | | | |
|---|---|---|---|
| Cadmium fluoride | 7790-79-6 | | $CdF_2$ |
| Cadmium molybdate | 13972-68-4 | Molybdic acid, cadmium salt (1:1) | $CdMoO_4$ |
| Cadmium nitrate | 10325-94-7 | Nitric acid, cadmium (2+) salt (1:2) | $Cd(NO_3)_2$ |
| Cadmium oxide | 1306-19-0 | | CdO |
| Cadmium sulphate | 10124-36-4 | Sulphuric acid, cadmium salt (1:1) | $CdSO_4$ |
| Cadmium sulphide | 1306-23-6 | Aurora yellow; cadmopur golden yellow N; cadmopur yellow: C.I. No. 77199; C.I. pigment orange 20; C.I. pigment yellow 37; greenockite<br><br>Capsebon | CdS |

## 1.2 Chemical and physical properties

Physical properties of the cadmium compounds considered in this monograph are given, when available, in Table II. Additional information on solubility is given below.

Cadmium metal - soluble in dilute nitric acid and in sulphuric acid

Cadmium acetate - very soluble in water and soluble in methanol

Cadmium carbonate - insoluble in water (Schindler, 1967), soluble in acids, ammonium salts and potassium cyanide

Cadmium chloride - soluble in water (140 g/100 ml at 20°C; 150 g/100 ml at 100°C) and slightly soluble in methanol (1.7 g/100 ml at 15.5°C) and ethanol (1.5 g/100 ml at 15°C); it forms hydrates containing 1, 2.5 and 4 molecules of water, respectively.

Cadmium fluoborate - extremely hygroscopic and very soluble in water and 95 percent ethanol (Stacey et al., 1960)

Cadmium fluoride - soluble in hydrogen fluoride (0.2 g/100 g at 14.2°C) (Jache & Cady, 1952) and in water (3.5 g/100 ml at 25°C) (Pascal, 1959)

Table II[a]

| Chemical Name | Atomic/mol. weight | Melting-point °C | Boiling-point °C | Crystal system | Density $g/cm^3$ | Refractive Index $n_D^{20}$ |
|---|---|---|---|---|---|---|
| Cadmium | 112.40 | 320.9 | 765 | hexagonal, silver-white metal | $8.642^{20}$ | 1.8 at 578 nm[c] |
| Cadmium acetate | 230.50 | 256 | | | 2.341 | |
| Cadmium carbonate | 172.41 | | | triagonal, white powder | $4.258^{4}$ | |
| Cadmium chloride | 183.32 | 568 | | hexagonal, colourless | $4.047^{25}$ | 1.65 at 589.3 nm |
| Cadmium fluoride | 150.40 | | 1758 | cubic, white | 6.33[b] | 1.56 at 589.3 nm |
| Cadmium molybdate | 272.34 | | | yellow plates | 5.347 | |
| Cadmium nitrate | 236.41 | 350 | | colourless solid | 2.45[d] | |
| Cadmium oxide | 128.40 | 900 (dec.) | 1559 (subl.) | cubic, brown | 8.15 | 2.49 at 670.8 nm |
| Cadmium sulphate | 208.46 | 1000 | | rhombic, white | $4.691^{20}_{4}$ | |
| Cadmium sulphide | 144.46 | 1750 at 100 atm | 980 (subl. in $N_2$) | hexagonal, yellow-orange | 4.82 | 2.506; 2.529 at 589.3 nm |

[a] Data from Weast (1975) unless otherwise specified.

[b] From Haendler & Bernard (1951).

[c] From Lyman (1961).

[d] From Pascal (1959).

Cadmium molybdate - slightly soluble in water and soluble in acids, ammonium hydroxide and potassium cyanide

Cadmium nitrate - very soluble in water (109 g/100 ml at 0°C; 326 g/100 ml at 60°C; 682 g/100 ml at 100°C) (Weast, 1975)

Cadmium oxide - insoluble in water and alkalis but soluble in acids and solutions of ammonium salts (Greene, 1974)

Cadmium sulphate - soluble in water (75.5 g/100 ml at 0°C; 60.8 g/100 ml at 100°C) (Weast, 1975) but barely soluble in methanol and ethanol (Pascal, 1959)

Cadmium sulphide - soluble in acids and in ammonium hydroxide (Greene, 1974) but barely soluble in water (0.00013 g/100 ml at 18°C) (Weast, 1975)

## 1.3 Technical products and impurities

Tentative specifications for cadmium metal issued in 1966 by the American Society for Testing and Materials (US Bureau of Mines, 1970) made the following requirements:

| Element | Percentage |
|---|---|
| Cadmium (by difference), minimum | 99.90 |
| Zinc, maximum | .035 |
| Copper, maximum | .015 |
| Lead, maximum | .025 |
| Tin, maximum | .01 |
| Silver, maximum | .01 |
| Antimony, maximum | .001 |
| Arsenic, maximum | .003 |
| Thallium, maximum | .003 |

Cadmium sponge when dispatched to customers has a moisture content of about 25 % when packaged in bags and 35% when packaged in drums. Even with this precaution, substantial oxidation occurs, and typical cadmium contents on a dry basis are 86% in bags and 92% in drums. A pure form of cadmium for electronic uses contains 0.001% or less of impurities.

Cadmium acetate is usually available as the hydrate $Cd(CH_3COO)_2 .2H_2O$ in technical or reagent grades.

Cadmium carbonate is available in a commercial grade which has a purity of about 98%, lead, zinc and iron being present as impurities. Higher purity grades are available for special applications.

Commercial cadmium chloride is a mixture of hydrates that approximates to the dihydrate ($CdCl_2.2H_2O$). The commerical grade of cadmium chloride available in the US typically contains about 51% cadmium and 0.005% each of iron and copper. There are higher purity grades available for specialized applications such as photographic chemicals and phosphors.

Cadmium nitrate with a purity greater than 99% can be obtained; typical impurities are chloride (0.005%), sulphate (0.005%), copper (0.005%), iron (0.002%),lead (0.005%), zinc (0.05%) and arsenic (0.001%).

The commercial grade of cadmium oxide available in the US has a reported purity of 99.7%, with lead and thallium as detectable impurities.

Commercial grade of cadmium sulphate reportedly contains about 49.5% cadmium; the theoretical cadmium content of $CdSO_4$ is 53.5%.

Because cadmium sulphide and cadmium sulphide-containing materials are used principally for their physical properties rather than for their chemical ones, the usual measures of product grading are seldom used. Although the commercial grade of cadmium sulphide, when not otherwise specified as a pigment of a phosphor, typically contains 98.8% cadmium sulphide and 0.7% cadmium sulphate, most products in which it occurs are more complex. Thus, cadmium yellow pigments are cadmium sulphide-zinc sulphide mixtures; cadmium lithopone pigments are co-precipitates of cadmium sulphide and barium sulphate; cadmium sulphoselenides are varied mixtures of cadmium sulphide, cadmium selenide and selenium sulphide; and the so-called mercadium pigments contain mercuric sulphide in combination with cadmium sulphide. The cadmium sulphide used in phosphors is usually a mixture with zinc sulphide and contains trace amounts of activators such as silver, copper or nickel.

## 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, page 19.

## 2.1 Production and use

Cadmium: The principal sources of cadmium are the sintering of flue dusts and the roasting of zinc ores. Some cadmium metal is also recovered as a by-product of the purification by distillation of slag zinc.

World production of cadmium was about 16.5 million kg in 1970 and had increased to 17 million kg by 1973 (Hague, 1973; Tewarte, 1973, 1975). US production in 1973 was 3360 thousand kg (Hague, 1973).

Canada, Japan, US, USSR and Zaire accounted for 74 percent of the world production in 1965. Other countries with appreciable production include Australia, Austria, Belgium, Bulgaria, Federal Republic of Germany, France, German Democratic Republic, Honduras, Ireland, Italy, Mexico, The Netherlands, Norway, Peru, Poland, Spain, Sweden, Yugoslavia and Zambia (Fairbridge, 1974; US Bureau of Mines, 1975).

In 1973, US imports of cadmium metal were 1.76 million kg and of cadmium ore and flue dust, 793 thousand kg. In the same year, US exports were 139 thousand kg (US Bureau of Mines, 1975).

Demand for cadmium in the US has averaged 5.67 million kg over the last few years and has been used in the following ways: 49% in metal plating, 18% in plastics stabilizers, 14% in pigments and 19% in miscellaneous uses (nickel-cadmium batteries, alloys) (Bureau of National Affairs, Inc., 1975).

Nearly all cadmium electroplating is carried out in baths formulated from cadmium metal and cadmium oxide dissolved in sodium cyanide solution, using a cadmium anode. the baths provide about 20% of the total amount of cadmium used in electroplating; the metal anodes account for the remaining 80%. The most important applications of this electroplating are in automotive and aircraft parts, electronic parts, marine equipment and industrial machinery. Cadmium electroplate, primarily on steel, is superior to that of zinc in providing resistance to corrosion. A general review of cadmium electroplating is given by Walker (1974).

The next largest use for cadmium is in the production of cadmium compounds that serve as stabilizers for plastics. The most common stabilizers are mixtures of cadmium and barium salts of long-chain fatty acids.

Another use of cadmium is in the preparation of cadmium sulphides, cadmium selenides and mixtures containing these salts for use as pigments (including phosphors). The phosphors require very pure starting materials, and cadmium oxide is preferred as the cadmium source.

Cadmium is used as the negative electrode in nickel-cadmium storage batteries found in industrial equipment, motor vehicles and many rechargeable household and biomedical appliances.

Cadmium-containing alloys are used for bearings where the high speeds and temperatures are excessive for tin or lead alloys. Such bearing alloys contain about 99% cadmium in combinations with nickel, silver and/or copper. Cadmium alloys used for soldering aluminium contain 10-95% cadmium, with zinc or silver as the other elements. Low-melting alloys of cadmium contain 8-40% of this metal in combination with bismuth, indium, tin and/or lead, and these alloys are used in a variety of applications (e.g., fire-protection fusible links, fusible cores for foundry moulds, holding irregular parts for machining, bending pipes and thin sections, soldering and sealing).

Other uses of cadmium that consume minor quantities include alloys for neutron shields and control rods for nuclear reactors. Spongy cadmium is used in the laboratory for the determination of nitrate.

Cadmium acetate: This compound can be prepared by treating cadmium nitrate with acetic anhydride (Stecher, 1968).

It is used to produce iridescent effects on porcelains and pottery and as a reagent for determination of sulphur, selenium and tellurium in cadmium electroplating (Stecher, 1968). It is also used in dyeing and printing textiles and in the purification of mercaptans from crude oils and gasolines (Greene, 1974).

Cadmium carbonate: Cadmium carbonate can be prepared by absorption of carbon dioxide in cadmium hydroxide solution, and this is believed to be the main commercial process.

Its major use is believed to be in fungicides. Cadmium carbonate is applied as a lawn and turf fungicide in concentrations of 3.0 and 5.3% as a wettable powder in combination with organic fungicides. The next most significant use is in the preparation of high-purity, specialized chemicals such as phosphors.

Cadmium chloride: The chloride is made by dissolving cadmium metal in hydrochloric acid and evaporating to dryness in

a stream of hydrogen chloride gas or by dissolving cadmium oxide or carbonate in hydrochloric acid.

It is believed that pesticides are the largest single use of the commercial grade and that higher purity cadmium chloride is used increasingly in photographic materials and phosphors. It is used in non-pasture turf fungicides.

Minor uses for the chloride include its applications in dyeing and in calico-printing of textiles, in the manufacture of thermoionic emission coatings for electronic vacuum tubes, as a lubricant ingredient and in the manufacture of special mirrors.

Cadmium fluoborate: This compound is prepared from aqueous solutions of fluoboric acid and cadmium metal, carbonate or oxide; it is the hexahydrate form (Stacey et al., 1960). Conventional methods of dehydration result in partial hydrolysis of the fluoborate ion and loss of volatile acidic components. It is more convenient and economical to supply 40-50% aqueous solutions (Halbedel, 1966).

Solutions of cadmium fluoborate are used in electroplating of metals.

Cadmium fluoride: Cadmium fluoride can be prepared by the reaction of cadmium carbonate with hydrofluoric acid. Its characteristics are similar to those of zinc fluoride, for which it may be substituted in certain phosphors. It is used as a glass ingredient and in nuclear reactor controls.

Cadmium molybdate: The molybdate forms when a solution of cadmium nitrate is treated with an alkaline molybdate solution (Sneed & Brasted, 1955). No information was available concerning its commercial uses.

Cadmium nitrate: Cadmium nitrate can be prepared by reacting cadmium oxide with nitric acid. It forms both a dehydrate and a tetrahydrate. The tetrahydrate, which is the major commercial form, is used principally in the manufacture of nickel-cadmium batteries. It has also been used as a turf fungicide.

Cadmium oxide: This compound is made commercially by distilling cadmium metal from a graphite retort and allowing the vapour to react with air.

Electroplating appears to be the largest use for cadmium oxide. Other important applications are in the manufacture of cadmium electrodes for alkaline storage batteries and in the synthesis of other cadmium salts.

Cadmium sulphate: The sulphate is made commercially as both the anhydrous ($CdSO_4$) and the hydrated salt ($3CdSO_4 .8H_2O$). The usual commercial production of these materials involves dissolution of the metal, oxide, carbonate or sulphide in sulphuric acid with subsequent cooling or evaporation to precipitate the salt. Cadmium sulphate is also made as an intermediate in the recovery of cadmium from zinc ore.

The principal uses of cadmium sulphate are in the manufacture of cadmium salts of long-chain fatty acids used as stabilizers for plastics (especially polyvinyl chloride) and in the manufacture of cadmium sulphide pigments (including phosphors), of cadmium lithopone pigments and of cadmium sulphoselenide pigments. Its use in medicinal preparations has been discontinued owing to its toxicity.

Cadmium sulphide: Cadmim sulphide is produced commercially by the reaction of hydrogen sulphide gas with a cadmium salt (usually cadmium sulphate).

Almost all of the cadmium sulphide produced in the US is used in pigments (including phosphors). These pigments, which range in colour from yellow to deep maroon, are used principally when heat stability (e.g., in plastics, coloured vulcanized rubber and some epoxy resins), alkali resistance (printing inks) and resistance to hydrogen sulphide blackening (paints and artists' colours) are needed. Other materials for which cadmium sulphide pigments have been found useful include glass, ceramics, textiles and paper.

The principal phosphor use of cadmium sulphide is in cathode-ray tube screens. Minor quantities are used in a variety of applications that benefit from the low energy level required to obtain visible light from this chemical. Phosphorescent tapes and markers, watch and instrument dials, interior decorations and theatrical effects are common uses. It is also used in X-ray fluorescent screens and body temperature gradient detectors.

Cadmium sulphide has been used as the active ingredient of shampoos designed for use in the treatment of seborrhoeic dermatitis of the scalp.

## 2.2 Occurrence

Reviews of the occurrence of cadmium in the environment have been published (Friberg et al., 1974, 1975; Organization for Economic Cooperation and Development, 1975).



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Natural environment: Cadmium is a relatively rare element in the earth's crust. Greenockite (cadmium sulphide) is the most common of its minerals, and it can be found in weathered ores are otavite (cadmium carbonate). In both forms it is associated with zinc and lead-zinc ores and is recovered as a by-product in their refining. Other minerals that contain cadmium are hawleyite, CdS; xanthocroite, $CdS(H_2O)_x$; cadmoselite, CdSe; and monteporrite, CdO (Fairbridge, 1974). Trace quantities of cadmium are also found in coals and oils.

Air: Cadmium can enter the air from a variety of manufacturing operations that involve either cadmium itself (e.g., production of copper-cadmium alloys) or zinc that contains cadmium as an impurity (e.g., smelting operations, galvanizing of steel). Cadmium can also enter the atmosphere when cadmium-plated scrap steel is remelted or from the incineration of waste plastics containing cadmium stabilizers and pigments. Smelting operations reportedly account for 87% of emissions to air, remelting of cadmium-plated steel for 9% and incineration for only 4% (Bureau of National Affairs, Inc., 1975).

Cadmium oxide and cadmium sulphate can also be found in atmospheric emissions from thermal processes involving cadmium.

In rural areas cadmium concentrations in ambient air are generally below 3 $ng/m^3$, but in large cities the yearly average may be up to 50 $ng/m^3$. In the vicinity of cadmium-emitting industries weekly or monthly means of about 300 $ng/m^3$ have been recorded (Friberg et al., 1974).

Cigarette smoke: Determinations of cadmium in cigarette tobacco indicate a level of 1.7 µg per cigarette. As much as 10% of the cadmium may pass into the mainstream smoke (Szadkowski et al., 1969). For a heavy smoker this could add significantly to the daily cadmium intake: it is estimated that smokers who inhale 20 cigarettes per day accumulate 0.5 mg cadmium in one year (i.e., about 1.5 µg/day) (Lewis et al., 1972).

Occupational exposure: Exposure to cadmium has been high in the past: cadmium concentrations of several milligrams per $m^3$ of air were reported (Friberg, 1950; Petrovic & Kalember, 1969; Petrovic et al., 1968; Tarasenko & Vorobjeva, 1972). In recent years, possible improvements to the working environment have been proposed in order to reduce exposure, and Piscator et al. (1976) reported that in the accumulator factory studied by Friberg (1950) present air concentrations of cadmium are about 0.04 $mg/m^3$.

The concentration of cadmium oxide in the pre-mould department of a smelter ranged from 0.074-0.09 mg/m$^3$, and 1.1 mg/m$^3$ were found in the retort department (Lemen et al., 1976). Cadmium sulphide has also been found as a contaminant in working atmospheres, at concentrations generally less than 0.1 mg/m$^3$ (Harada, 1973). Concentrations of 0.08-25 mg/m$^3$ cadmium sulphate have been reported in the USSR (Tarasenko & Vorobjeva, 1972).

Water: Cadmium can enter surface waters from natural sources and from a variety of manufacturing operations that involve either cadmium itself (e.g., electroplating for corrosion protection) or zinc that contains a cadmium impurity (e.g., galvanizing of steel). It can enter the aqueous environment when spent solutions from plating operations are discarded. Ore tailings and washings from the production of refined cadmium metal are also potential sources of cadmium in nearby surface waters. Another source is the application of phosphate fertilizers, which have been found to contain traces of cadmium.

The level of non-polluted city water is less than 1 µg/l, but, as a result of industrial discharge and of the use of metal or plastic pipes, this level may increase to 10 µg/l (Friberg et al., 1974). It has been reported (Yamagata & Shingematsu, 1970) that in polluted rivers cadmium is often undetectable in the water itself but that high concentrations can be found in bottom sediments. Cadmium salts, such as cadmium carbonate, cadmium chloride and cadmium sulphate, may appear in surface waters as a result of run-off from industrial processes.

Soil and uptake in plants: In non-polluted areas, cadmium concentrations in soil are generally below 1 µg/g; whereas in polluted areas in Japan, concentrations of 1-70 µg have been found in rice fields (Friberg et al., 1974). Both superphosphate fertilizers and sewage sludge used as fertilizer may add considerable quantities of cadmium to soil. Two important foodstuffs, wheat and rice, have been shown to have increased uptakes of cadmium when grown in soil containing large amounts (Friberg et al., 1974).

Sources of soil pollution by cadmium have been estimated as follows: remelt steel operations (25%), stabilizers (24%), pigments (18%), batteries (6%), alloys and miscellaneous uses (12%), sewer sludge landfill (3%), sewer sludge incineration (3%) and solid waste incineration (4%) (Bureau of National Affairs, Inc., 1975).

Air, water, soil; The relative significance of some of the above applications in the US in 1968 has been estimated (Fulkerson et al., 1973; US Environmental Protection Agency, 1975), and the results are given in Table III.

Table III

| Source | Quantity processed (thousand kg of cadmium) | Emissions to: | Estimated emissions (thousand kg) |
|---|---|---|---|
| Primary processing | | | |
| Ore extraction | 2150 | Air,<br>water, soil | 0.2<br>Not available |
| Ore concentration and metal production | 5800 | Air | 950 |
| Conversion of metal to products | 6000 | Air | 15 |
| Product use | Not available | Air, water, soil | 16 |
| Recycle or disposal | - | Air, water, soil | 1000 |
| Miscellaneous | | | |
| Fossil fuel combustion | 310 | Air | 90-320 |
| Phosphate fertilizer application | 20 | Water, soil | Up to 22 |
| Motor oil use | - | Air, water, soil | 0.8 |

In principle, all of the cadmium and/or its salts, such as cadmium chloride, used as stabilizers and pigments in plastics could enter the environment, a process particularly facilitated by incineration. Thus, disposal of plastics could contribute to pollution by cadmium.

Food: There is little doubt that food is the main source of cadmium intake in non-occupationally exposed persons. The presence of cadmium in a wide range of both fresh and tinned foodstuffs has been reported by Klein & Wichmann (1945) and by Friberg et al., (1974, 1975). Schroeder & Balassa (1961) suggested that the main intake in the US diet was from sea-foods and grain products; vegetables were another source (Schroeder & Balassa, 1963).

Meat, eggs, fish and milk products generally have a low content of cadmium, less than 0.01 µg/g wet weight, whereas internal organs, especially liver and kidney, may contain much more; concentrations of up to 1 µg/g wet weight have been reported in animal organs. Some salmon meat was reported to contain more than 3 µg/g cadmium (Friberg et al., 1974), however, the analytical method used was not reported; internal organs from fish and shellfish may also contain high amounts (Banat et al., 1972; Oelschlaeger & Bestenlehner, 1975).

Vegetable products generally contain more cadmium than do animal products. Rice and wheat, two important foodstuffs, may contain from 0.01-01 µg/g in areas regarded as non-polluted; but in polluted areas in Japan, cadmium concentrations of 0.1-1 µg/g have commonly been found (Friberg et al., 1974).

The following table gives a comparison of the daily intakes in several countries (Friberg et al., 1974):

| County | µg Cd/day |
|---|---|
| Czechoslovakia | 60 |
| Federal Republic of Germany | 48 |
| Japan (non-polluted areas) | 47-59 |
| Romania | 38-64 |
| US | 4-92 |

General human exposure: In the general populations, the main exposure is via food; and, except in the vicinity of some cadmium-emitting industries, cadmium in the ambient air does not contribute significantly. The daily intake via drinking-water is generally low but may be higher in contaminated areas or when

cadmium-containing material contaminates tap-water. Smoking involves the inhalation of relatively small amounts of cadmium; but since it is highly absorbed from the lungs, in heavy smokers the absorbed amount may be of the same magnitude as that absorbed from food.

## 2.3 Analysis

General reviews of the analytical methods for cadmium are given by Friberg et al., 1974, 1975). An evaluation of analytical techniques for trace metals, including cadmium, in marine waters has been published (Lai, 1974).

The most common method is atomic absorption spectrophotometry, both flame and flameless methods. Extraction into organic solvents, ion-exchange separation or other methods of pre-treatment are often necessary. Blood, urine and some foodstuffs, in which cadmium concentrations are normally extremely low, previously presented analytical problems; interference from salts, e.g., sodium chloride, was the major problem; and many of the earlier data on the occurrence of cadmium in different media cannot be relied upon. Duing the last few years many of these analytical difficulties seem to have been overcome, and it is now possible to determine by flameless methods concentrations of less than 1 ng/g in blood and urine and less than 10 ng/g in foods (Kjellstrom et al., 1974 a,b; Linnman et al., 1973).

Other useful techniques are neutron activation (Linnman et al., 1973; Ljumggren et al., 1971) and emission spectroscopy (Tipton et al., 1963). Anodic stripping voltametry and other electrochemical methods appear to be very useful for determination of cadmium in water (Whitnack & Sasselli, 1969), but more data are needed to evaluate their usefulness for the determination of cadmium in biological samples. The dithizone method (Church, 1947), which was previously the most commonly used method, is accurate, but the sensitivity is relatively low.

# 4. Comments on Data Reported and Evaluation

## 4.1 Animal data

Single or repeated subcutaneous injections of several inorganic cadmium compounds (cadmium chloride, sulphate, sulphide and oxide) result in the development of local sarcomas in rats. Local tumours were also produced in rats by intramuscular injection of cadmium powder and cadmium sulphide.

Interstitial-cell tumours of the testis were observed following testicular atrophy in rats and mice given subcutaneous injections of soluble cadmium salts (cadmium sulphate and cadmium chloride). The pituitary glands of these animals showed castration changes.

Oral studies in mice and rats were inadequate for evaluation. No adequate long-term inhalation studies of carcinogenicity were available to the Working Group.

## 4.2 Human data

Available studies indicate that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man. In addition, one of these studies suggests an increased risk of respiratory tract cancer.

# Chloramphenicol

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

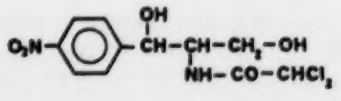
Chem. Abstr. Reg. Serial No.: 56-75-7

Chem. Abstr. Name: [R-(R*, R*)]-2,2-Dichloro-N-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamide

D-(-)-Threo-2-dichloroacetamido-1-ρ-nitrophenyl-1,3-propanediol; D-threo-N-dichloroacetyl-1-ρ-nitrophenyl-2-amino-1,3-propanediol; D-threo-(-)-2,2-dichloro-N-[β-hydroxy-α-(hydroxymethyl)-ρ-nitrophenethyl]acetamide: D-threo-N-(1,1'-dihydroxy-1-ρ-nitrophenylisopropyl)-dichloroacetamide; D-(-)-threo-ρ-nitrophenyl-1-dichloroacetamido-2-propanediol-(1,3)

Alficetyn; Ambofen; Amphicol; Amseclor; Aquamycetin; Austracol; Biocetin; Biophenicol; CAF; CAM; CAP; Catilan; Chemicetina; Chlomin; Chomycol; Chloramex; Chloramsaar; Chlorasol; Chlora-Tabs; Chloricol; Chloroamphenicol; Chlorocaps; Chlorocid; Chlorocol; Chloromycetin; Chloronitrin; Chloroptic; Chloro-25 Vetag; Cidocetine; Ciplamycetin; Cloramficin; Cloramicol; Cloramidina; Clorocyn; Cloromisan; Clorosintex; Comycetin; Cylphenicol; Desphen; Detreomycine; Dextromycetin; Doctamicina; Embacetin; Emetren; Enicol; Enteromycetin; Erbaplast; Ertilen; Farmicetina; Fenicol; Globenicol; Glorous; Halomycetin; Hartfenicol; Intramycetin; Isicetin; Ismicetina; Isophenicol; Isopto Fenicol; Juvamycetin; Kamaver; Kemicetina; Kemicetine; Klorita; Leukomycin; Levomicetina; Levomycetin; Loromisan; Mediamycetine; Micloretin; Micochlorine; Micoclorina; Microcetina; Mycinol; Novochlorocap; Novomycetin; Novophenicol; Oftalent; Oleomycetin; Opelor; Ophtochlor; Otachron; Otophen; Pantovernil; Paraxin; Pentamycetin; Quemicetina; Rivomycin; Romphenil; Septicol; Sificetina; Sintomicetina; Sintomycetine; Stanomycetin; Synthomycetine; Synthomycine; Tevcocin; Tifomycin; Tifomycine; Treomicetina; Unimycetin; Veticol

### 1.2 Chemical formula and molecular weight




$C_{11}H_{12}Cl_2N_2O_5$ Mol. wt: 323.1

## 1.3 Chemical and physical properties of the pure substance

(a) Description: White to greyish-white needles with bitter taste.

(b) Melting-point: 150.5-151.5°C (sublimes in high vacuum)

(c) Spectroscopy data: $\lambda_{max}$ 278 nm ($E^{1}_{1}$ = 298) (in water)

(d) Optical rotation: $[\alpha]_D^{27}$ + 18.6° (4.86% in ethanol)

(e) Identity test: Methods of identification are given in the British Pharmacopoeia (British Pharmacopoeia Commission, 1973)

(f) Solubility: 1.g dissolves in 400 ml water or 6 ml propylene glycol at 25°C; very soluble in methanol, ethanol, butanol, ethyl acetate, acetone; fairly soluble in ether

(g) Stability: Aqueous solutions are stable if protected from light

(h) Reactivity: The nitro group is readily converted to the amine by reduction.

## 1.4 Technical products and impurities

Chloramphenicol is listed in the British Pharmacopoeia (British Pharmacopoeia Commission, 1973) and is often formulated as the cinnamate, palmitate or sodium succinate salt. Data on physical properties of these salts are given by Cole (1969). Preparations are available as capsules (250 mg), ear-drops (5% solution in propylene glycol), eye-drops (0.5% solution) or eye-ointment (1% chloramphenicol). Chloramphenicol palmitate or cinnamate are water-insoluble powders formulated to overcome the bitter taste of chloramphenicol; on hydrolysis they release the free drug; 1.7 g of the palmitate are equivalent to 1.0 g chloramphenicol.

USP grade chloramphenicol is available in the United States; chloramphenicol capsules containing 90-120% of the labelled amount of active ingredient are available in doses of 50, 100 and 250 mg. Chloramphenicol ointment (1%) for ophthalmic use contains 90-130% of the labelled amount of active ingredient; an ophthalmic solution (0.5%) is available as a sterile, dry mixture of chloram phenicol and suitable buffers and contains 90-130% of the labelled amount of chloramphenicol (US Pharmacopeial Convention, Inc., 1975). USP grade chloramphenicol palmitate is sold as a suspension for

oral administration, and chloramphenicol sodium succinate is prepared for injection (American Society of Hospital Pharmacists, 1971).

Chloramphenicol is available in Japan in the form of tablets, capsules, syrups and for injection. Chloramphenicol succinate is also made up for injection, and the stearoyl glycolate is sold as a syrup (Fukai, 1974).

In Europe, chloramphenicol is available in forms for ophthalmic and otic use, for injection, in capsules for oral use, in suppositories, as a syrup, and in combination with vitamins (Bundesverband der Pharmazeutischen Industrie, 1969; Council of Europe, 1971; Dictionnaire Vidal, 1975).

## 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p. 17.

### 2.1 Production and use

Chloramphenicol is an antibiotic produced by Streptomyces venezuelae, an organism first isolated by Burkholder in 1947 from a soil sample collected in Venezuela (Ehrlich et al., 1947). The crystalline antibiotic substance was isolated by Bartz in 1948 (Goodman & Gilman, 1970), and in 1949 its structural determination (Rebstock et al., 1949) and chemical synthesis (Controulis et al., 1949) were reported.

The method believed to be used for commercial production involves the following steps: Condensation of para-nitrobenzoyl chloride with ethyl malonate to give para-nitroacetophenone; bromination in acetic acid to form para-nitro-α-bromoacetophenone; reaction of this with hexamethylene tetramine, followed by hydrolysis to give para-nitro-α-aminoacetophenone; acetylation of the amine group, followed by condensation with formaldehyde to give an hydroxymethyl group alpha to the amine group; treatment with aluminum isopropylate to reduce the keto group to a secondary alcohol; and, after deacetylation, condensation of the amine group with methyl dichloroacetate to give chloramphenicol (Anon., 1969).

Commercial production of chloramphenicol was first reported to the US Tariff Commision in 1948 (US Tariff Commission, 1949). In 1973 only two US companies reported production, and imports through the principle US customs districts in that year were reported to

have been 1.6 thousand kg (US Tariff Commission, 1974). Total US sales of chloramphenicol in its various forms for use in human medicine are estimated to be in the order of 6000 kg annually, mostly in capsule form for oral ingestion.

In 1971 a plant using a fermentation process started production in Japan. The process resulted from the discovery and isolation of a new strain of microbe and is claimed to be superior to the synthetic process since separation of stereoisomers is not required (Anon., 1972). There are currently five producers of chloramphenicol in Japan (Anon., 1974). Production between 1969 and 1972 was in the range of 27-75 thousand kg per year and in 1973 amounted to 42 thousand kg (Ministry of Health and Welfare, 1973).

There are reported to be producers of chloramphenicol in the Federal Republic of Germany, France, Italy, Spain, Switzerland and the United Kingdom (Chemical Information Services Ltd., 1975).

The commercial production of chloramphenicol in 1948 made available for the first time a broad-spectrum antibiotic effective against both Gram-positive and Gram-negative bacteria. Rickettsiae and organisms of the psittacosis-lymphogranuloma group are also sensitive to chloramphenicol; most fungi and yeasts are resistant.

Chloramphenicol is still mainly used for the treatment of Salmonella infections, as well as for many other infectious diseases (Dunne et al., 1973). The dose of chloramphenicol given to adults with typhoid fever is 2 g initially, followed by 1 g every six hours for 4 weeks, while the doses used for other infections are usually lower. For rickettsial diseases, the first dose of chloramphenicol is 50 mg/kg bw, followed by 1 g every 8 hours or 0.5 g orally every 4 hours.

Chloramphenicol has also been used in veterinary medicine, functioning as a broad-spectrum antibiotic treatment against many bacteria and certain viruses and rickettsiae (Stecher, 1968). It should not be used for any purpose that might result in the presence of residues in food for human consumption (FAO/WHO, 1969).

## 2.2 Occurrence

Although chloramphenicol is produced by Streptomyces venezuelae and has recently been isolated from a microbe in Japan, there are no data on its occurrece in nature.

In some countries food regulations require withdrawal periods in animals so as to avoid antibiotic residues in the final product. No figures on levels of chloramphenicol found in foods were available to the Working Group.

### 2.3 Analysis

Colorimetric methods for the determination of chloramphenicol have been described (Doll, 1955; Glazko et al., 1949a; Masterson, 1968). A microbiological method is given in The US Pharmacopeia (US Pharmacopeial Convention, Inc., 1975); an almost similar one is outlined by Banerjee et al. (1973). An ultra-violet absorption method for analysis of chloramphenicol preparations was described by Summa (1965), who also compared microbiological, polarographic and spectophotometric methods. Chloramphenicol may also be determined by gas chromatography of its trimethylsilyl derivative (Janssen & Vanderhaeghe, 1973; Margosis, 1970). The use of combined gas chromatography-mass spectrometry for determination of chloramphenicol, thiamphenicol and their metabolies in urine is described by Nakagawa et al. (1975) (limit of detection, 0.05 mg/l).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

No adequate tests of the carcinogenicity of chloramphenicol were available to the Working Group.

### 4.2 Human data

The available case reports suggest that aplastic anaemia due to chloramphenicol use is associated with subsequent development of leukaemia.

# Chloromethyl Methyl Ether*

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. No.: 107-30-2
CMME: chloromethyl ether[1]; dimethylchloroether; methyl chloromethyl ether

### 1.2 Chemical formula and molecular weight

$ClCH_2OCH_3$ $C_2H_5ClO$ Mol. wt: 80.5

### 1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless liquid

(b) Boiling-point: 59°C at 760 mm

(c) Density: $d_4^{20}$ 1.0605

(d) Refractive index: $n_D^{20}$ 1.3974

(e) Solubility: Miscible with ethanol and ether and many other organic solvents

(f) Stability: Decomposes in the presence of water and in hot ethanol

(g) Volatility: Highly volatile

### 1.4 Technical products and impurities

Commercial chloromethyl methyl ether (CMME) contains a minimum of 95% of the active ingredient. CMME typically contains several precent of bis(chloromethyl)ether as an impurity (Collier, 1972).

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* Considered by the Working Group in Lyon, June 1973.

1 This name is more properly used for bis(chloromethyl)ether.

## 2. Production, Use, Occurrence and Analysis

### (a) Production and use[1]

CMME can be produced by the reaction of methyl alco hyde and anhydrous hydrogen chloride.

No information is available in world production of CMME. The number of US producers has dropped from three in 1969 to one in 1973. In 1967, one company was reported to be making CMME in the Federal Republic of Germany. It seems likely that CMME is produced as a chemical intermediate in other countries.

CMME, both in a purified form and as a component of chloromethylating reaction mixture which may contain gross amounts of bis(chloromethyl)ether, is used as an intermediate in the synthesis of chloromethylated compounds which are often subsequently converted to aminated compounds by reaction with organic amines. One such utilization, and probably the largest single use for CMME, is in the preparation on ion-exchange resins. A modified polystyrene resin is chloromethylated and then treated with a tertiary amine or with a polyamine. Other chloromethylated compounds of commercial significance which may involve CMME in their manufacture include chloromethyl diphenyl oxide, 1-chloromethyl-naphthalene, di(chloromethyl) diphenyl oxide, di(chloromethyl)toluene and dodecylbenzyl chloride. No data are available on the total production of these chemicals or on the amount, if any, produced from CMME, since they are largely used as intermediates.

### (b) Occurrence

CMME has not been reported to occur as such in nature. Since it hydrolyzes readily, it would not be expected to remain as such for protracted periods in waste streams from plants where it is produced or used.

CMME is listed together with 13 other chemicals in the US Federal Register (US Government, 1973) as being subject to an Emergency Temporary Standard on certain carcinogens under an order made by the Occupational Safety and Health Administration, Department of Labor on 26 April, 1973

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[1] Data from Chemical Information Services, Stanford Research Institute, USA.

(c) Analysis

The determination of CMME in air has been reported: CMME is hydrolyzed, and the products are determined turbidimetrically and colorimetrically (Vinogradova, 1962). Several methods for the detection of alkylating agents have been described (Preussmann et al., 1969; Sawicki & Sawicki, 1969).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Chloromethyl methyl ether (CMME) is almost invariably contaminated by bis(chloromethyl)ether (BCME), and the latter may be responsible for at least part of the observed carcinogenic activity. Such contaminated CMME has been found to be carcinogenic on subcutaneous injection in the mouse and possibly to be an initiator for mouse skin tumours. Inhalation in mice and subcutaneous injection in the rat produced equivocal evidence of carcinogenic activity.

### 4.2 Human data

One study based on 4 cases of oat cell lung cancer observed amongst 111 workers exposed to CMME (and its associated BCME impurity), followed for 5 years, suggests an increased risk of lung cancer.

## Calcium Chromate

### 1. Chemical and Physical Data

#### 1.1 Identity and solubility

| Chemical Name | Formula | Chem. Abstr. No | Aqueous Solubility | Synonyms |
|---|---|---|---|---|
| Chromium | Cr | 7440-47-3 | Insoluble | - |
| Calcium chromate | $CaCrO_4$ | 10060-08-9 | Slightly soluble | Chromic acid ($H_2CrO_4$), calcium salt (1:1)<br>Calcium chromate (VI)<br>Calcium chrome yellow<br>C.I. No. 77223[1]<br>C.I. pigment yellow 33[1]<br>Gelbin yellow ultramarine<br>Pigment yellow 33<br>Steinbuhl yellow |
| Chromic oxide | $Cr_2O_3$ | 1308-38-9 | Insoluble | Anadomis green<br>Casalis green<br>Chrome green (hydrated)<br>Chrome ochre<br>Chrome oxide<br>Chromia<br>Chromic oxide green<br>Chromium oxide<br>Chromium (III) oxide<br>Chromium oxide green<br>chromium oxide pigment<br>Chromium sesquioxide<br>C.I. No. 77288 & 77278[1]<br>11661 Green[1]<br>Green chrome oxide<br>Green chromium oxide<br>Green cinnabar<br>Green oxide of chromium<br>Green oxide of chromium OC-31<br>Green rouge |

* Considered by the Working Group in Lyon, December 1972.

| Chemical Name | Formula | Chem. Abstr. No | Aqueous Solubility | Synonyms |
|---|---|---|---|---|
| | | | | Guignet's green (hydrated chromic oxide)<br>Leaf green<br>Levanox green GA<br>Oil green<br>Oxide of chromium<br>Pure chromium oxide green 59[1]<br>Ultramarine green |
| Chromium dioxide | $CrO_2$ | 12018-01-8 | Insoluble | Chromium (IV) oxide |
| Chromium trioxide | $CrO_3$ | 1333-82-0 | Soluble | Chromic acid<br>Chromic (VI) acid<br>Chromic anhydride<br>Chromic trioxide<br>Chromium oxide |
| Lead chromate | $PbCrO_4$ | 7758-97-6 | Insoluble | Canary chrome yellow 40-225P<br>Chrome lemon<br>Chrome yellow<br>C.I. No. 77600[1]<br>Chromic acid ($H_2CrO_4$), lead (II) salt (1:1)<br>C.I. Pigment Yellow 34[1]<br>Cologne yellow<br>C.P. Chrome yellow light<br>C.P. Chrome yellow medium<br>C.P. Chrome yellow primrose<br>King's yellow<br>Lead chromate (VI)<br>Leipzig yellow<br>Lemon yellow<br>Paris yellow<br>Plumbous chromate |
| Potassium dichromate | $K_2Cr_2O_7$ | 7778-50-9 | Soluble | Dichromic acid dipotassium salt<br>Potassium bichromate |

[1] Colour Index number.

| Chemical Name | Formula | Chem. Abstr. No | Aqueous Solubility | Synonyms |
|---|---|---|---|---|
| | | | | Potassium dichromate (VI)<br>Red potassium chromate |
| Sodium dichromate | $Na_2Cr_2O_7$ | 10588-01-9 | Soluble | Dichromic acid disodium salt<br>Sodium bichromate<br>Sodium dichromate (VI) |

The following compounds were included in the monograph but no information on "Use and Occurrence" is available:

| | | | | |
|---|---|---|---|---|
| Barium chromate | $BaCrO_4$ | 10294-40-3 | Insoluble | Chromic acid, barium salt<br>C.I. No. 77103[1]<br>C.I. pigment yellow 31<br>Baryta yellow<br>Lemon yellow<br>Permanent yellow<br>Steinbuhl yellow<br>Ultramarine yellow |
| Chromium acetate | $Cr(COOCH_3)_3.H_2O$ | 1066-30-4 | Soluble | Acetic acid, chromium (III) salt |
| Chromium carbonate | $Cr_2O_3.xCO_2.4H_2O$ | 6449-00-9 | Slightly soluble | Carbonic acid, chromium (III) salt |
| Chromium phosphate | $CrPO_4$ | 7789-04-0 | Insoluble | Phosphoric acid, chromic (III) salt |
| Potassium chromate | $K_2CrO_4$ | 7789-00-6 | Soluble | Natural potassium chromate<br>Chromic acid, dipotassium salt |
| Sodium chromate | $Na_2CrO_4$ | 7775-11-3 | Soluble | Chromic acid, disodium salt |
| Strontium chromate | $SrCrO_4$ | 7789-06-2 | Slightly soluble | Chromic acid, strontium salt |
| Zinc chromate hydroxide | $Zn_2CrO_4(OH)_2.H_2O$ | 12206-12-1 | Slightly soluble | Zinc yellow<br>Buttercup yellow |

[1] Colour Index number.

The compounds considered in this monograph are essentially insoluble in organic solvents with the single exception of chromium trioxide which is soluble in alcohol and ether. In aqueous systems the solubilities of the chromium salts vary greatly even within families of related materials (see Table).

## 1.2 Stability

The compounds of chromium considered are all stable materials, although those having water of hydration may be expected to gain or lose water as a function of temperature.

Both chromium trioxide and sodium and potassium dichromate are powerful oxidizing agents and should be handled with care.

## 2. Production, Use, Occurrence and Analysis

### (a) Use

Chromium: The metal is made commercially in the US by two processes: (1) an electrolytic method in which a chromium-containing electrolyte (prepared by dissolving a high carbon ferrochromium in a solution of sulphuric acid and chromium potassium sulphate) is subjected to electrolysis; (2) an aluminothermic reduction method in which chromic oxide is reduced with finely divided aluminium. Chromium metal is available in the US as electrolytic chromium (99.5% Cr), aluminothermic chromium (98.5% Cr) and ductile chromium (99.99% Cr).

In 1970, US production of chromium metal and metal alloys other than ferrochromium alloys was reported to have been 31 million pounds (about 75% was made by the electrolytic method). This included production of chromium briquets, exothermic chromium additives and miscellaneous chromium alloys, in addition to chromium metal.

Chromium metal and metal alloys other than ferrochromium alloys are used primarily in stainless and heat-resisting steel and alloy steel.

They are used in alloys to impart strength, hardness and resistance to corrosion, oxidation, wear and heat.

Calcium chromate: Calcium chromate is produced commercially by the reaction of calcium chloride with sodium chromate. Hydrated forms can be made, but the anhydrous salt is the only product of commercial significance. It is believed that calcium

chromate is largely used as a corrosion inhibitor and as a depolarizer in batteries.

The use of calcium chromate in protective coatings for steel and light metals is sometimes reported as a pigment use, but the primary function of calcium chromate in these products is that of a corrosion inhibitor.

Chromic oxide: The anhydrous material is produced industrially by heating chromic hydroxide, by heating dry ammonium dichromate, or by heating sodium dichromate with sulphur and washing out the sodium sulphate. The hydrated material is made commercially be calcining sodium dichromate with boric acid and hydrolysing the resulting chromium borate. Both the anhydrous and hydrated oxide could be present in products which have been coloured green by their addition.

US production of the most important type of chromic oxide, chromic oxide green, was reported to be about 13.2 million pounds in 1971.

The major portion of chromic oxide (anhydrous and hydrated) is used as a pigment. A substantial portion is also used in metallurgy and, to a lesser extent, as a catalyst, in refractory brick, and as a chemical intermediate.

Anhydrous chromic oxide is the most stable green pigment known and is used in applications requiring heat, light and chemical resistance (e.g., in glass and ceramics). It is used in dyeing polymers, and its resistance to alkalis makes it a valuable colorant for latex paints. It finds special use in colouring Portland cement, in green granules for asphalt roofing and in camouflage paints.

Metallurgical grade anhydrous chromic oxide is used in the manufacture of chromium metal and aluminium-chromium master alloys. It is used as a catalyst in the preparation of methanol, butadiene and high density polyethylene. In refratory brick, chromic oxide is used as a minor component to improve performance.

Hydrated chromic oxide is also used as a green pigment, especially for automotive finishes.

Chromium dioxide: Chromium dioxide is made by the thermal decomposition of chromium trioxide, but it is not sold on the open market since apparently the only use is in high-energy magnetic tapes. The tapes are reported to give improved fidelity at lower speeds than conventional magnetic tapes based on acicular ferric oxide. At present, the amount of chromium dioxide used

in these tapes is probably only a few million pounds, but consumption may increase in the future.

Chromium trioxide: Chromium trioxide is produced industrially by the reaction of sodium dichromate with sulphuric acid.

Its major use is in chromium plating, particularly in the production of automobiles. Additional uses in other metal-finishing operations include aluminium anodizing, which has been used extensively on military aircraft assemblies; chemical conversion coatings, which provide both decorative and corrosion protection effects; and the production of phosphate films on galvanised iron or steel. Important non-plating uses of chromium trioxide include use as a corrosion inhibitor for ferrous alloys in recirculating water systems, as an oxidant in organic synthesis, and in catalyst manufacture. Small amounts of chromium trioxide are also used to modify the properties of basic magnesite refractories.

Lead chromate: Lead chromate can be produced by reacting sodium chromate with lead nitrate, or by reacting lead monoxide with chromic acid solution. Details of various commercial procedures for the manufacture of lead chromates are not generally revealed by the producers. By varying the proportion of the reactants, either lead chromate ($PbCrO_4$) or basic lead chromate ($PbO.PbCrO_4$) can be produced. High lead chromate content is associated with the more yellow pigments, while increasing the basic lead chromate content gives orange and red pigments.

Production data for lead chromate are not available, however it is undoubtedly produced by the pigments industries of most industrialised countries. The combined production of chrome yellow and chrome orange is reported for the US, however, and amounted to 64.9 million pounds in 1970.

To prevent lead poisoning in small children who eat chips of peeling paint from old housing, the US Environmental Protection Agency has ordered a ban on interstate shipments of paints for domestic use containing more than 0.06% lead, effective from 31 December 1973. This ban will undoubtedly significantly reduce the US consumption of lead chromate pigments and will thereby reduce whatever contribution lead chromate presently makes to lead and chromium pollution problems.

Potassium dichromate: Potassium dichromate is produced industrially by roasting chrome ore with potassium carbonate, or preferably by reacting sodium dichromate with potassium chloride.

Combined production of potassium dichromate and potassium chromate in 1966 was estimated at 6-8 million pounds, with the potassium dichromate believed to be the more important chemical industrially.

Potassium dichromate was once the leading chromium compound, but it has been largely replaced in many applications by sodium dichromate. The present market for potassium dichromate appears to consist of a large number of small volume applications. Probably the largest uses are photomechanical processing, chrome pigment production and wood preservative formulations.

Sodium dichromate: Sodium dichromate is produced industrially by the reaction of sulphuric acid on sodium chromate, which is obtained by calcining a mixture of chromite ore (a chromium iron oxide), limestone and soda ash.

Since sodium dichromate is the primary chrome chemical from which all of the others are made, it could occur as a water pollutant from chrome chemicals plants or in losses during pigment production or leather tanning operations. However, in the US maximum permissible chromium concentration standards have been set for hexavalent chromium ion which have resulted in fairly widespread adoption of recycling and conservation practices.

Combined US production of hydrated sodium dichromate and hydrated sodium chromate was 276.4 million pounds in 1971. Sodium dichromate is the principal commercial product and is preferred to the more expensive sodium chromate.

Consumption of sodium dichromate is believed to be largely in chrome pigments production, chromium trioxide production, and in leather tanning and industrial water treatment.

Chrome pigments are used in paints, printing inks, for colouring paper, rubber, linoleum, composition floor tile, and in practically all other applications for coloured pigments.

The second largest usage for sodium dichromate is in the production of chromium trioxide (see the discussion of chromium trioxide for more imformation).

(b) Analytical methods

Many methods have been used to determine chromium. At present the three most sensitive methods are: gas chromatography (Taylor, 1971; Sievers et al., 1967); spark source mass spectroscopy (Evans & Morrison, 1968); and graphite furnace atomic

atomic absorption determination of chromium are described by Feldman et al. (1967) and Moten (1970). Iida & Fuwa (1967) used a multichannel flame spectrometer. The detection limits for the four methods are $10^{-14}$ g, 5 x $10^{-11}$ g, $10^{-11}$ g and $10^{-9}$ g, respectively. Gas chromatography has been successfully employed by Savory et al./(1969); gas chromatography mass spectrometry by Wolf et al. (1972); chemiluminescence by Seitz et al. (1972); and X-ray spectrochemistry by Gofman (1962). Gorsuch (1962) has shown that dry ashing of organic samples results in little loss of chromium; however, low-temperature ashing is preferable. Livingston & Wacker (1971) have summarised methods for metal decontamination of chemicals and lab ware. Cellular analysis for chromium may be accomplished by ion microscope or laser microprobe techniques. Neutron activation analysis is adapted for sub-nanogram detection (Coleman et al., 1967).

(c) Occurrence

Chromium

Natural environment: Chromium is found in nature only in the combined state and not as the element. It is derived mainly from chromite ($FeO.Cr_2O_3$), which is found in considerable quantities in Rhodesia, Russia, South Africa, New Caledonia and the Philippines and contains 40-50% chromium (Bidstrup & Case, 1956).

Air: Falk (1970) found a chromium content of 15 ng/$m^3$ in the particulate of air samples taken in the US in 1964 and 1965. Generally, the concentration in air is between 0.002 and 0.02 ug/$m^3$. Stocks (1960) found 0.9-21.5 ng/$m^3$ in 23 localities in Northern England and Wales in 1956-58.

Water: In the sea, the concentration is less than 1µg/kg, but annually, 6.7 x $10^6$ kg of chromium are added to the oceans (Bowen, 1966). In the rivers, the concentration lies between one and ten µg/kg. The permissible level of $Cr^{6+}$ in drinking-water is 50 µg/kg (WHO, 1963).

Soil: Chromium is present in the soil at levels which vary from traces to 250 mg/kg as chromic oxide (Robinson, 1914), and particularly in soils derived from basalt or serpentine (Bowen, 1966).

Food: Chromium is present in low concentrations in most foods (Morgan, 1972).

Calcium chromate: Calcium chromate does not occur naturally. There is a possibility that it may occur in wastes associated with its production or use.

Chromic oxide: Chromic oxide and hydrated chromic oxide do not occur in nature.

Chromium dioxide: Chromium dioxide does not occur in nature.

Chromium trioxide: Chromium trioxide does not occur in nature. It may occur as a water pollutant in the effluent from chrome chemicals plants. It may also occur as a polluting effluent from chrome-plating and other metal-treating shops. However, maximum permissible chromium concentration standards have been set in the US for hexavalent chromium which have resulted in fairly widespread adoption of recycling and conservation practices.

Lead chromate: Lead chromate occurs in nature as the minerals crocoite and phoenicochroite. Because lead chromate is insoluble in water, it seems unlikely that it occurs in significant quantities in the waste streams from plants producing or using it.

Potassium dichromate: Potassium dichromate does not occur in nature.

Sodium dichromate: Sodium dichromate does not occur in nature.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

In many experiments, various chromium compounds have been shown to induce tumours in mice and rats. Calcium chromate has been found to be carcinogenic by several routes of administration, producing epithelial tumours of the lung by intrabronchial implantation and sarcomas by intramuscular and intrapleural administration to rats.

Of the other chromium salts tested in the rat by intramuscular and intrapleural administraton, chromic chromate and zinc chromate hydroxide were highly evocative of sarcomas at the site of injection in the rat, whilst barium chromate, lead chromate, chromic acetate and sodium dichromate were inactive or practically

inactive. Strontium chromate was tested only by intramuscular implantation and evoked many local sarcomas.

Studies involving oral administration of chromic acetate in mice and rats which gave negative results were considered inadequate because the level of exposure was low.

## 4.2 Human data

There is an excessive risk of lung cancer among workers in the chromate-producing industry. It is likely that exposure to one or more chromium compounds is responsible, but the identity of this or these is not known.

There is no evidence that non-occupational exposure to chromium constitutes a cancer hazard.

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

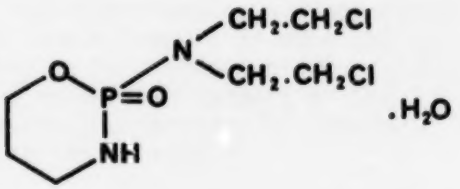
Chem. Abstr. Reg. Serial No.: 50-18-0

Chem. Abstr. Name: N,N-Bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxaphosphorin-2-amine, 2-oxide monohydrate

B 518; 1-bis(2-chloroethyl)amino-1-oxo-2-aza-5-oxaphosphoridine monohydrate; 2-[bis(2-chloroethyl)amino]-1-oxa-3-aza-2-phosphocyclohexane 2-oxide monohydrate; 2-[bis(2-chloroethyl)amino]tetrahydro-[2H]-1,3,2-oxazaphosphorine 2-oxide monohydrate; [bis(chloro-2-ethyl)-amino]-2-tetrahydro-3,4,5,6-oxazaphosphorine-1,3,2-oxide-2 monohydrate; N,N-bis(2-chloroethyl)-N'-(3-hydroxypropyl)phosphorodiamidic acid intramolecular ester monohydrate; bis(2-chloroethyl)phosphoramide cyclic propanolamide ester monohydrate; N,N-bis(β-chloroethyl)-N', O-propylenephosphoric acid ester amide monohydrate; N,N-bis(β-chloroethyl)-N', O-trimethylenephosphoric acid ester diamide monohydrate; CB-4564; cyclic N', O-propylene ester of N,N-bis(2-chloroethyl) phosphorodiamidic acid monohydrate; cyclophosphamid; 2-[di(2-chloroethyl)amino]-1-oxa-3-aza-2-phosphacyclohexane-2-oxide monohydrate; N,N-di(2-chloroethyl)amino-N,O-propylene phosphoric acid ester diamide monohydrate; NSC-26271

B 518; Clafen; Cyclophosphamidum; Cyclophosphan; Cyclophosphane; Cyclophosphanum; Cytophosphan; Cytoxan; Endoxan; Endoxana; Endoxan-Asta; Endoxan R; Enduxan; Genoxal; Mitoxan; Procytox; Semdoxan; Sendoxan; Senduxan

### 1.2 Chemical formula and molecular weight




$C_7H_{15}Cl_2N_2O_2P.H_2O$

Mol. wt: 279.1

## 1.3 Chemical and physical properties of the pure substance

(a) Description: A fine, white, odourless or almost odourless, crystalline powder with a slightly bitter taste. If the water of crystallization is removed by high vacuum or drying agents, it becomes an oily, half-liquid mass.

(b) Melting-point: 49.5-53°C, determined on the substance without previous drying (British Pharmacopoeia Commission, 1973).

(c) Spectroscopy data: IR spectrum ($cm^{-1}$) 3385 (N-H) (in dichloroethane) (Rauen, 1964)

(d) Solubility: Soluble at 20°C in 25 parts of water and in 1 part of ethanol; also soluble in benzene, chloroform, dioxane and glycols; slightly soluble in ether and acetone; insoluble in carbon tetrachloride and carbon disulphide (British Pharmacopoeia Commission, 1973; White, 1959).

(e) Stability: Darkens on exposure to light. Aqueous solutions may be kept for a few hours at room temperature, but hydrolysis occurs at temperatures above 30°C, with removal of chlorine atoms (British Pharmaceutical Codex, 1973).

## 1.4 Technical products and impurities

Cyclophosphamide is available in the US as a USP grade in the form of tablets containing 25 and 50 mg active ingredient, and in a crystalline hydrate form for injection packaged in ampoules in strengths of 100, 200 and 500 mg to be administered after solution in sterile water (Medical Economics Co., 1974). Cyclophosphamide crystalline hydrate USP, used to formulate the tablets and injections, contains 100±5% cyclophosphamide. The tablets contain 100±10% of the labelled amount of cyclophosphamide, and the injection, a sterile mixture with sodium chloride, contains 100±5% of the labelled amount of cyclophosphamide (US Pharmacopeial Convention, Inc., 1970).

In Europe, cyclophosphamide tablets are available in 10 and 50 mg strengths. The crystalline hydrate form for injection is available in ampoules containing 100, 200, 500 and 1000 mg active ingredient, to be administered after solution in sterile water (Bundesverband der pharmazeutischen Industrie, 1969; Dictionnaire Vidal, 1975; Pullom, 1968-69).

In Japan, tablets containing 50 mg and ampoules for injection in 100, 200 and 500 mg strengths are available (JAPTA, 1973).

## 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p. 17.

### 2.1 Production and use

Cyclophosphamide can be prepared by treating N,N-bis(β-chloroethyl)-phosphamide dichloride with propanolamine in the presence of trimethylamine and dioxane (Arnold & Bourseaux, 1958).

The major producer of cyclophosphamide is in the Federal Republic of Germany. Some of the production is exported to the US, where one company has formulated and marketed the drug since 1959. Total US sales are approximately 600 kg annually. Cyclophosphamide is also produced in Finland and in the UK (Chemical Information Services, Ltd, 1975) where production was estimated to have reached a few hundred kg annually in the early seventies. Cyclophosphamide is also marketed in Japan.

Cyclophosphamide is the most widely used antineoplastic agent in the treatment of various neoplastic diseases, including malignant lymphomas, multiple myeloma, leukaemias, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, carcinoma of the breast and malignant neoplasms of the lung. It has been used in combination with other agents to treat lymphoreticular and some other tumours (Greenwald, 1973; Livingston & Carter, 1970). The usual initial dose is about 10 mg/kg bw daily given intravenously for 2-5 days or 1-5 mg/kg bw daily given orally (Medical Economics Co., 1974).

Cyclophosphamide is used in human medicine as an immunosuppressive agent in a variety of non-malignant diseases, e.g., rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, polymyositis, scleroderma, uveitis, idiopathic pulmonary hemosiderosis, glomerulonephritis, idiopathic nephrotic syndrome in children, chromic interstitial pneumonia, psoriatic arthritis, Behoet's disease, pyoderma gangrenosum, myasthenia gravis, multiple sclerosis, idiopathic thrombocytopenic purpura, macroglobulinaemia and cryoglobulinaemia in Sjogren's syndrome, pemphigus vulgaris and bullous pemphigoid (Essig et al., 1974; Madved & Maxwell, 1974; O'Donohue, 1974; Rubens-Duval et al., 1974; Steinberg et al., 1972). Recently, patients suffering from chronic hepatitis have also been treated with cyclophosphamide for long periods of time (Naccarato et al., 1974). It is increasingly being used as a immunosuppressive agent following organ transplantation (Starzl et al., 1973).

Cooperative trials with many hundreds of patients have been conducted to test its applicability in rheumatoid arthritis, nephrotic syndrome in children and systemic lupus erythematosus (Anon., 1974; Cooperating Clinics Committee, 1970; Mackay et al., 1974).

Cyclophosphamide has also been tested as an insect chemosterilant (LaBreoque & Gouck, 1963). The US Department of Agriculture has shown it to be an effective agent for the removal of wool in the chemical shearing of sheep, and at the time of preparation of this monograph, application had been made to the US Food and Drug Administration for approval of its use in this way.

## 2.2 Occurrence

Cyclophosphamide is not known to occur in nature.

## 2.3 Analysis

Methods for the determination of cyclophosphamide include: one based on estimation of nitrogen, phosphorous or chloride content; colorimetric analysis, based on the intensity of a cobalt thiocyanate-cyclophosphamide complex or by use of 4-(4'-nitrobenzyl)pyridine after hydrolysis; titrimetric analysis, after precipitation of the digested material by quinoline and citric-molybdic acid solution; and infrared spectrometry. The method with the greatest degree of specificity is infrared spectrometry based on the characteristic stretching frequency of the phosphorous-oxygen bond at 9.5 μm (Boughton et al., 1972).

A gas-liquid chromatographic determination of cyclophosphamide in raw material, tablets and drug-containing vials ready for injection has been reported by Boughton et al. (1972). Under the conditions specified by the authors, a chromatogram with three peaks is found: the two major peaks were identified by mass spectrometry as intact cyclophosphamide (the 90% peak, with a molecular ion of 260 mass units) and as dehydrohalogenated cyclophosphamide (the 9% peak, with a molecular ion of 224 mass units). Duncan et al. (1973) described a mass spectrometric method for studying the distribution of cyclophosphamide in human tissue and body fluids. A concentration of at least 1μg/ml of body fluid was required in order to obtain a low-resolution spectrum in which the drug could be recognized: the spectrum is characterized by a weak molecular ion peak at m/e 260, with the most abundant fragment ion occurring at m/e 211, corresponding to loss of the $.CH_2Cl$ radical.

## 4. Comments on Data Reported and Evaluations

### 4.1 Animal data

Cyclophosphamide is carcinogenic in mice and rats following its intraperitoneal injection, in rats following its intravenous injection and in mice following its subcutaneous injection, in doses similar to those used in clinical practice. It produced mainly lung and lymphoreticular tumours, and also tumours of the liver and reproductive organs, sarcomas and squamous-cell carcinomas of the skin.

### 4.2 Human data

The available case reports in which tumours were reported to have occurred in patients treated with cyclophosphamide provide insufficient evidence to determine if there is an increased risk of cancer following the therapeutic use of this drug, with the possible exception of cancer of the bladder.

# Diethylstilboestrol (Stilboestrol)

## 1. Chemical and Physical Data

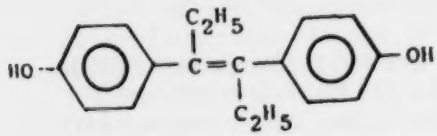
### 1.1 Synonyms and trade names*

Chem. Abstr. No.: 56-53-1

DEB; DES; 4,4'-(1,2-diethyl-1,2-ethenediyl)bis-phenol; α,α'-diethylstilbenediol; α,α'-diethyl-4,4'-stilbenediol; trans-α,α'-diethyl-4,4'-stilbenediol; diethylstilbesterol; diethylstilboesterol; trans-diethylstilbesterol; trans-diethylstilboesterol; diethylstilbestrol; trans-diethylstilbestrol; trans-diethylstilboestrol; 4,4'-dihydroxy-α, β-diethylstilbene; 3,4-(4,4'-dihydroxyphenyl)-hex-3-ene; 3,4-bis(p-hydroxyphenyl)-3-hexene; stilbesterol; stilboesterol; stilbestrol

Bio-des; Climaterine; Comestrol estrobene; Cyren; Cyren A; Cyren B; Di-Estryl; Distilbene; D Oestromon; Domestrol; Estilben; Estilbin MCO; Estril; Estrobene; Estrosyn; Follidiene; Fonatol; Grafestrol; Hi-Bestrol; Idroestril; Microest; Milestrol; Neo-distilbene; Neo-Oestranol; New-Oestranol I; Oestrogenine; Oestromenin; Oestromensil; Oestromensyl; Oestromienin; Oestromon; Palestrol; Percutatrine Oestrogénique Iscovesco; Protectona; Sedestran; Serral; Sexocretin; Sibol; Sintestrol; Stil; Stilbetin; Stilboefral; Stilboestroform; Stilkap; Stil-Rol; Synerstrin; Synestrin; Synthoestrin; Syntofolin

### 1.2 Chemical formula and molecular weight



$C_{18}H_{20}O_2$

Mol. wt: 268.3

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* Trade names include mixtures containing diethylstilboestrol.

## 1.3 Chemical and physical properties of the pure substance

(a) Description: White platelets (from benzene)

(b) Melting-point: 169-172°C

(c) Solubility: Practically insoluble in water; soluble at 25°C in 95% ethanol (1 in 5), chloroform (1 in 200), ether (1 in 3); soluble in acetone, dioxane, ethyl acetate, methyl alcohol, vegetable oils and aqueous solutions of alkali hydroxides.

## 1.4 Technical products and impurities

The diethylstilboestrol (DES) used commercially is the trans-isomer; the cis-isomer is obtained with difficulty and tends to revert to the trans form (Merck & Co., 1968). DES is available in the United States as a USP grade in tablets, suppositories and in a form suitable for injection. It is also available as the diphosphate ester derivative in the form of tablets and as an aqueous solution of its sodium salt (Kastrup, 1973).

DES was formerly available in the US as implants for use in beef cattle and sheep and as an additive in cattle feeds. Rulings of the US Food and Drug Administration (FDA) have prohibited these uses.[1]

# 2. Production, Use, Occurrence and Analysis

## 2.1 Production and use[2]

The oestrogenic properties of diethylstilboestrol (DES) were first described by Dodds et al. (1938). A number of synthesis routes have since been developed, all starting with either desoxyanisoin, anisoin, anisole or p-methoxypropiophenone and involving various rearrangements. In a method first reported in 1943, anethole hydrobromide is converted to an intermediate ether using sodamide in liquid ammonia, and this is converted to DES by heating with potassium hydroxide in ethylene gyclol. Commercial production of DES was first reported in the US in

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1 A US Court of Appeal, in January 1974, ruled that the FDA had not met all legal requirements in establishing its position. Thus, the legality of the ban has not as yet been resolved.

2 Data from Chemical Information Services, Stanford Research Institute, USA.

1941, when less than 227 kg were produced (US Tariff Commission, 1945). Although three or more companies have reported production to the US Tariff Commission in several subsequent years, separate data on US production and sales have been published only infrequently. Production data were last reported in 1952, when 1,800 kg were produced (US Tariff Commission, 1953). A total of five US companies are believed to have been producing DES in 1972, but one of of these companies has since stopped production. One of the manufacturers also produces the diphosphate ester derivative. Total US sales of DES and its diphosphate ester derivative for use in human medicine are estimated to be less than 500 kg annually.

In 1972, a total of 3,053 kg of DES were reported to have been imported through the principal US customs districts (US Tariff Commission, 1973). This was a sharp reduction from the 5,355 kg reported for 1971 (US Tariff Commission, 1972) and the 5,604 kg reported for 1970 (US Tariff Commission, 1971).

DES is one of the least expensive and most widely used oestrogens. Both DES and its diphosphate ester derivative find use in human medicine for treatment of such conditions as amenorrhea, breast carcinoma, hypogenitalism, menopausal syndrome, postmenopausal oesteoporosis, postpartum breast engorgement, prostatic carcinoma and senile vaginitis. In such applications, DES may be used in combination with androgens and with other medicinals, e.g., vitamin and bactericides (Kastrup, 1972).

In July 1972, as a result of the report of a drug efficacy study group, the FDA concluded that a group of drugs, which included DES vaginal suppositories, were effective in the treatment of post-menopausal and senile vulvovaginitis, atrophic vaginitis, pruritus vulvae caused by atrophic changes in the vulval epithelium dyspareunia associated with an atrophic vaginal epithelium, and for use prior to plastic pelvic surgery in menopausal cases. However, the FDA concluded that there was no substantial evidence of effectiveness if the drug was indicated for mammary hypoplasia. DES has also been used in the past for treatment of threatened abortions, but because of the appearance of genital tract cancers in the female offspring of women who took the drug during their pregnancy (see section 3.3, "Observations in man", for additional information), new cautions against the use of the drug by pregnant women have been issued (US Environmental Protection Agency, 1972a)

DES has been used in the US in recent years for postcoital contraception, although this application has not been officially approved by the FDA. In September 1973 the FDA, in an effort to restrict the use to birth control, announced that new drug

applications will be required for this use and that the manufacturers must provide brochures which will explain the risks and benefits of the drug to users (US Environmental Protection Agency, 1973).

Data on production of DES in the countries of Western Europe are not available but production and sales are known to be concentrated in a small number of companies. Total sales of DES in hormone specialties in Western Europe in 1972 are estimated to have been less than 80 kg. Sales in Spain represented approximately 65% of the total, with lesser amounts sold in Belgium, the Federal Republic of Germany, France, Italy, The Netherlands and the United Kingdom.

In the US formerly, DES was implanted (usually in the neck) in male chickens to caponize them chemically and to improve fattening and finishing. The FDA banned such implants in 1959 when residues of DES were found in edible poultry tissue (US Congress, 1973). It was also widely used in the US as a feed additive and as an ear implant to fatten, promote growth and to increase the feed efficiency of beef cattle and sheep. Because of concern about the appearance of residues of DES in food derived from the animals and about the observed carcinogenic properties of DES in test animals, the FDA banned the use of DES in animal feed in August 1972 (US Environmental Protection Agency, 1972b)[1] and banned the use of DES implants on April 27, 1973 (Anon., 1973).

Veterinary uses of DES include replacement therapy for underdeveloped females, incontinence, vaginitis of spayed bitches, hypertrophy of prostate in dogs and other applications (Merck & Co., 1968). Although no data are available on the quantity of DES consumed in these ways, it is believed that the largest volume used was in feed additives and implants.

In some European countries the use of such oestrogenic hormones as growth promoters in animals is forbidden; in others they are still used.

## 2.2 Occurrence

Diethylstilboestrol does not occur in nature.

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[1] A US Court of Appeal, in January 1974, ruled that the FDA had not met all legal requirements in establishing its position. Thus, the legality of the ban has not as yet been resolved.

## 2.3 Analysis

Methods for the analysis of diethylstilboestrol in tablets or feeds are given in the section "General Remarks on the Sex Hormones", p.42.

## 4. Comments on Data Reported and Evaluation

According to Campbell & Cummins (1951) and Benson (1957), the great majority of reported cases of breast cancer in men treated with oestrogens for cancer of the prostate are in fact metastases of the prostatic tumour. The report of O'Grady & McDivitt (1969), however, describes a case of primary carcinoma of the breast with Paget's disease of the nipple in a man who had received long-term treatment with DES for carcinoma of the prostate. The most recent paper on this topic (Bulow et al., 1973) reviews 30 cases reported in the world literature between 1946 and 1972. Among the 16 who were treated with DES alone, with total doses varying from 200-44,200 mg, the breast tumour appeared from 1 to 57 months after the start of treatment. On the basis of histological and biochemical investigations, 6 of the tumours were considered to be new primaries and 10 to be metastases.

## 4. Comments on Data Reported and Evaluation[1]

### 4.1 Animal data

Diethylstilboestrol (DES) was tested in mice by oral administration, local application and subcutaneous injection, in mice, rats, hamsters and squirrel monkeys by subcutaneous implantation and in hamsters by subcutaneous injection. Its administration to mice resulted in an increased incidence of mammary and lymphoid tumours in both males and females, and of interstitial-cell tumours of the testis in males and cervical and vaginal tumours in females, including those exposed only on the first day of life. In rats, increased incidences of pituitary, mammary and bladder tumours were observed. In hamsters, a high incidence of renal tumours was observed in castrated males and females and in intact males, but not in intact females. In squirrel monkeys, malignant mesotheliomas of the uterine serosa were observed.

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1 This section should be read in conjunction with the section, "General Conclusions on Hormones", p. 235.

DES treatment in most cases increased the incidence of mammary tumours in strains of mice having a spontaneous incidence of these tumours, which may be related to the presence of a virus; testicular tumours occurred in strains having a particular genetic susceptibility to such tumours. No evidence of a possible role of a virus has been shown in rats. Bladder tumours occurred only in rats in which bladder calculi were present.

In most cases, an accurate assessment of the effective carcinogenic dose on implantation studies is not possible. However, in oral administration studies, the lowest statistically significant dose ($P<0.01$) producing mammary carcinomas in mice was about 0.15 ug/day (6ug/kg bw/day). This dose is similar to that used in humans in the control of menopausal symptoms by DES (10 ug/kg bw/day) and 30 times less than the dose given for the control of mammary or prostatic cancer (300 µg/kg bw/day).

## 4.2 Human data

The administration of diethylstilboestrol to women during pregnancy is associated with an increased risk of vaginal or cervical adenocarcinoma in their exposed female offspring. There may also be an increased risk of endometrial carcinoma in women with gonadal dysgenesis treated with this drug. It is possible that the administration of the drug therapeutically to men with carcinoma of the prostate increases the risk of breast cancer.

# Hematite and Iron Oxide*

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. No. (iron oxide): 1309371

Iron oxide: Ferric oxide; Sesquioxide of iron

Iron ore: Haematite (hematite, red iron ore, blood stone); Limonite (brown hematite, brown iron ore, brown ironstone clay)

It should be noted that haematite (or hematite in the American spelling) may have two distinct meanings. It may be used to describe an iron plus silicon ore, to which miners are exposed (see Stewart & Faulds, 1934; Faulds & Stewart, 1956) or as a synonym for ferric oxide, $Fe_2O_3$ (see Saffiotti et al., 1968).

### 1.2 Chemical formula and molecular weight

$Fe_2O_3$ Mol. wt: 159.70

### 1.3 Chemical and physical properties of the pure substance

(a) Description

Iron oxide: A dense, dark red powder or lumps; after strong ignition it is steel grey.

Iron ore: The most important iron ore is haematite, which is a mineral found mainly in two forms: red haematite or red iron ore, which consists mainly of $Fe_2O_3$ and contains approximately 70% of iron; brown haematite or brown iron ore, which consists mainly of hydrated sesquioxide of iron (limonite) and contains approximately 42% of iron.

Less commonly occurring forms of haematite include: (i) brilliant lustre (a steel grey crystalline variety, known also as looking-glass ore, iron glance, or specular iron ore);

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* Considered by the Working Group in Geneva, December 1971.

(ii) micaeous iron ore consisting of thin scales or plates; (iii) speculous ore formed by the interaction of steam and ferric chloride in volcanic regions; (iv) soft red ore which is earthy; (v) red ochre and rouge.

(b) Melting-point: Fe, 1535°C; $Fe_2O_3$, 1565°C

(c) Specific gravity: Fe, 7.85; $Fe_2O_3$, 5.12-5.24

(d) Solubility: Fe and $Fe_2O_3$ are soluble in acids and insoluble in water.

(e) Chemical reactivity: Iron is rapidly oxidized in damp or salty air (rust).

(f) Technical products and impurities: The absence of phosphorus in red haematite (red iron ore) makes it a valuable source of iron. Although haematite consists mainly of ferric oxide, the most commonly mined ores contain between 10% and 12% silica.

## 2. Production, Use, Occurrence and Analysis

### 2. Use and Occurrence

(a) Use

Haematite is a source of iron. The very wide uses of iron ore are well known.

Hueper (1955) listed the following occupations as entailing the risk of inhalation of dust and fumes of iron and its various alloys and compounds: iron-ore miners; arc welders; grinders; polishers; silver finishers; metal workers. To this list boiler scalers should perhaps be added (Harding & Massie, 1951).

According to Stewart & Faulds (1934), haematite mining was judged to be a relatively healthy occupation until the introduction of pneumatic drills in 1913 into the West Cumberland mines and the great increase in airborne dust which their use entailed. Thereafter, the incidence of emphysema, bronchitis and tuberculosis among the iron-ore miners increased.

(b) Analytical methods

Iron was analysed by atomic absorption spectrophotometry in baking powder (Holak, 1970) and in alcoholic beverages (Meredith et al., 1970) and by the ring oven technique for airborne particulates (West, 1966).

(c) Occurrence

Deposits of haematite are found in: (i) parts of Lancashire, Cumberland and Cornwall in the British Isles; (ii) Northern Spain in the region of Bilbao; (iii) Minnesota, USA, near Lake Superior; (iv) Italy, in the Apuan Alps between Massa and Lucca; (v) Sweden; (vi) Ukraine in Krivoi Rog iron district and Kertch district.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Ferric oxide given by inhalation or by intratracheal route has not been found to be carcinogenic in the hamster, the mouse or the guinea-pig.

### 4.2 Human data

On the basis of epidemiological evidence, exposure to haematite dust may be regarded as increasing the risk of lung cancer development in man. The risk is manifest in underground workers but not surface workers, and it is not known whether the excess risk is due to radioactivity in the air of mines, the inhalation of ferric oxide or silica, or to a combination of these or other factors. There is no evidience that iron-ore dust (haematite) or ferric oxide influence the incidence of cancers at sites other than the lungs.

# Isopropyl Alcohol and Isopropyl Oils

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Isopropyl alcohol

Chem. Abstr. Services Reg. No.: 67-63-0

Chem. Abstr. Name: 2-Propanol

Dimethyl carbinol; dimethylcarbinol; IPA; isohol; isopropanol; petrohol; PRO; propan-2-ol; iso-propanol; sec-propyl alcohol; secondary propyl alcohol

Alcosolve 2; Avantine; Lutosol

Isopropyl oils

Not applicable

### 1.2 Chemical formula and molecular weight

Isopropyl alcohol

$CH_3$-CHOH-$CH_3$

$C_3H_8O$ Mol. wt: 60.1

Isopropyl oils

Not applicable

### 1.3 Chemical and physical properties of the pure substance

Isopropyl alcohol

From Weast (1976), unless otherwise specified

(a) Description: Colourless liquid (Wickson, 1968)

(b) Boiling-point: 82.4°C

(c) Melting-point: -89.5°C

(d) Density: $d_4^{20}$ 0.7855

(e) Refractive index: $n_D^{20}$ 1.3776

(f) Spectroscopy data: $\lambda_{max}$ 181 nm ($E_1^1$ = 103) (gaseous form); infra-red, ultra-violet, nuclear magnetic resonance and mass spectra have been tabulated by Grasselli (1973).

(g) Solubility: Soluble in acetone, very soluble in benzene; miscible with water, ethanol and ether

(h) Volatility: Vapour pressure is 32.4 mm at 20°C (Wickson, 1968).

Isopropyl oils

Not applicable

## 1.4 Technical products and impurities

Isopropyl alcohol

Three commercial grades of isoproyl alcohol available in the US, which differ mainly in water content, are 91 by volume %, 95 by volume %, and anhydrous (Wickson, 1968). A typical specification for anhydrous isopropyl alcohol is: purity, 99.8 by volume %, min.; water, 0.1 wt % max.; acidity (as acetic acid), 0.002 wt %, max.; colour, Pt-Co, 5 max.; distillation range, 1°C; initial boiling-point, 81.3°C min.; dry-point, 83.0°C max.; nonvolatile matter, 0.002 g/100 ml max.; water miscibility at 20°C, 10 volumes; density, 0.786-0.787; and appearance, bright and clear.

Isopropyl alcohol is also available as a National Formulary grade containing 99-100.5% of the pure chemical for solvent use. Isopropyl rubbing alcohol contains 68-72 by volume % of the pure chemical, water, possibly perfume oils, and colour additives certified by the US Food and Drug Administration for use in drugs (National Formulary Board, 1970).

Isopropyl alcohol is also available in the US as a cosmetic grade (91 by volume % and anhydrous), which contains perfume as a masking agent, as an electronic grade, with low conductivity,

and as reagent grades for use in analytical laboratory methods (Wickson, 1968).

In Japan, product specifications for commercial grade isopropyl alcohol are similar to those for the anhydrous grade in the US.

Isopropyl oils

Isopropyl oils are a by-product of isopropyl alcohol manufacturer. Gas chromatograpic and mass spectrometric analysis of isopropyl oils produced by the older, strong-acid process [see section 1.2 (a)] showed it to be a mixture composed primarily of trimeric and tetrameric polypropylene, with small amounts (less than 1% each) of benzene, toluene, alkyl benzenes, polyaromatic ring compounds, hexane, heptane, acetone, ethanol, isopropyl alcohol and isopropyl ether. Fluorescence of the residue after successive distillations of the isopropyl oils yielded spectra characteristic of benzanthracene. Chromatographic fractions of the residue from isopropyl oil distillation contained 86.8% carbon and 12.0% hydrogen (depending on the method of determination) (Weil et al., 1952).

The isopropyl oils produced in the newer, weak-acid process [see section 2.1 (a)] may contain polymers of lower molecular weight than those produced by the strong-acid method (NIOSH, 1976).

## 2. Production, Use, Occurrence and Analysis

For background information on this section, see preamble, p. 27. A review on isopropyl alcohol has been published (Wickson, 1968).

### 2.1 Production and use

Isopropyl alcohol

(a) Production

The reaction of propylene and sulphuric acid was used to prepare isopropyl alcohol by Berthelot in 1855; however, the product was first recognized as isopropyl alcohol in 1862, when Kolbe identified and named it (Wickson, 1968).

Isopropyl alcohol is manufactured in the US by an indirect hydration technique in which a fraction containing 40-60% propylene that is isolated from refinery exhaust gases is reacted with sulphuric acid (Lowenheim & Moran, 1975). In an older process (strong-acid), 88-93% sulphuric acid was reacted with propylene gas at 25-60°C for a long time. In a newer process (weak-acid), which has replaced the strong-acid process, propylene gas is absorbed in 60% sulphuric acid at 85°C for a short reaction time (NIOSH, 1976).

In Europe and Japan, the indirect hydration process is being replaced by a direct hydration process in which propylene reacts directly with water in the presence of a catalyst. In Japan, 66% of the isopropyl alcohol is produced by the newer direct hydration process.

Commercial production of isopropyl alcohol was begun in the US in 1921, when three companies manufactured a total of 84 thousand kg (US Tariff Commission, 1922). In 1974, five US companies reported a total production of 880 million kg isopropyl alcohol (US International Trade Commission, 1976a). Preliminary data for 1975 indicate a total US production of 700 million kg (US International Trade Commission, 1976b). In 1975, the US exported 56 million kg isopropyl alcohol to the following countries (% of total exports received): Australia (2.5), Belgium (8.2), Brazil (3.8), Canada (2.5), Colombia (4.6), the Federal Republic of Germany (9.3), Italy (3.7), Mexico (8.6), the Netherlands (26.7), Venezuela (17.8) and at least fourteen other countries (12.3) (US Department of Commerce, 1976). US imports are negligble.

Six countries in western Europe produced an estimated 360 million kg isopropyl alcohol in 1975, as follows (% of total production): The Federal Republic of Germany (19.3), France (15.2), Italy (2.5), The Netherlands (29.0), Spain (8.3), and the UK (25.7). About 85 million kg were imported and about 90 million kg exported in these countries in that year.

Isopropyl alcohol has been produced commercially in Japan for over thirty years. In 1975, three Japanese companies produced a combined total of 58 million kg isopropyl alcohol. About 10 million kg were exported to east Asia (Korea, Taiwan, and Philippines) in that same year (The Chemical Daily Co. Ltd, 1976; Ministry of International Trade and Industry, 1976).

About 2 million kg were imported into Australia in 1975-76.

(b) Use

Estimated use of isopropyl alcohol in the US in 1975 was as follows: for acetone manufacture, 40% as a solvent, 35%, in a manufacture of other chemicals, 10%, in drug and cosmetic formulations, 5%, miscellaneous uses, 7%, and exports, 3% (Anon., 1975).

In the production of acetone, isopropyl alcohol may be dehydrogenated catalytically at 400°C to give acetone and hydrogen (major process) or oxidized at high pressure to give acetone and hydrogen peroxide.

The second main use of isopropyl alcohol is as a solvent; it is used to extract and/or purify numerous natural products, such as oils, gums, shellacs, waxes, kelp and pectin. One potential use is as a solvent in the manufacture of fish protein concentrate. Isopropyl alcohol is used as a solvent for synthetic resins, e.g., coatings such as phenolic varnishes and nitrocellulose lacquers (Lowenheim & Moran, 1975; Wickson, 1968).

The third principal use is in the manufacture of other chemicals, such as isopropyl acetate, isopropylamine, di-isopropylamine, herbicidal esters, isopropyl xanthate, isopropyl myristate, isopropyl palmitate, isopropyl oleate, aluminium isopropoxide and isopropyl ether (Wickson, 1968).

Isopropyl alcohol is also used as solvent in drug and cosmetic formulations and is the major component of rubbing compounds used as solvents and rubefacients (National Formulary Board, 1970). Its use in cosmetics has generally been limited to highly scented or relatively inexpensive products (Wickson, 1968).

Other reported applications of isopropyl alcohol include its use as a denaturant in special industrial solvents; in windshield-wiper concentrates, aerosol windshield de-icers and automobile petrol antifreeze mixtures; in aerosol home and garden insecticides, glass cleaners and other household specialities; as a coolant in beer manufacture; as a cleaning and drying agent in the manufacture of electronic tubes; as a de-icer for aircraft propellers; and as a fuel ingredient in refrigerator-car heaters (Wickson, 1968).

Use of isopropyl alcohol in western Europe in 1975 has been estimated as follows: as a source for acetone production, 46%; as a solvent in surface coatings, 20%; in other solvent usage, 15%; and for other miscellaneous uses, 19%.

In Japan, isopropyl alcohol is used as a solvent in surface coatings (25-30%) and inks (20%) and for other uses (50-55%).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to isopropyl alcohol does not exceed an eight-hour time-weighted average of 400 ppm (980 mg/$m^3$) in the working atmosphere in any eight-hour work shift of a forty-hour work week (US Occupational Safety & Health Administration, 1976); a ceiling of 800 ppm (1960 mg/$m^3$) was determined during a sampling time of 15 minutes (NIOSH, 1976). An estimated 141,000 employees may be exposed occupationally to isopropyl alcohol in the US (NIOSH, 1976).

In Australia, 980 mg/$m^3$ has also been recommended as the maximum in the working atmosphere.

The US Food and Drug Administration requires that isopropyl alcohol residue levels, after its use as an extractant, may not exceed 50 mg/kg in spice oleoresins, paprika oleoresin or annatto extract, 6 mg/kg in lemon oil, and 2.0% by weight in hops. The use of isopropyl alcohol as a defoaming agent is limited to the processing of beet sugar and yeast. When it is used as a synthetic flavouring substance and adjuvant, isopropyl alcohol must be used in the minimum quantity required to produce the intended effect. When it is used as a diluent in colour additive mixtures for marking foods, no residues may remain on the food (US Food & Drug Administration, 1976b).

## Isopropyl oils

### (a) Production

Isopropyl oils are produced as by-products in the reaction of propylene and sulphuric acid during the manufacture of isopropyl alcohol and consist of the residue after distillation. The older, indirect hydration, or strong-acid, process utilized concentrated sulphuric acid (88-93%) as a reactant. The reaction with propylene took place in a mixture of isopropyl sulphates at 25-60°C. The reaction time was long and produced isopropyl oils containing compounds with high molecular weight [see section 1.4] (NIOSH, 1976). One US factory which began production in 1943 utilized a concentration of 85-86% sulphuric acid (Anon., 1976).

A direct catalytic hydration, or weak-acid, process has replaced the strong-acid process in the US; with this method, a concentration of 60% sulphuric acid is used as a catalyst to

absorb and react with the propylene gas. The reaction is maintained at 85°C, and reaction time is reported to be very short, thus producing ispropyl oils that may contain polymer oils of low molecular weight, although an analysis of the material has not been reported [see section 1.4] (NIOSH, 1976). One US company currently uses a concentration of 67-70% sulphuric acid in its weak-acid process (Anon., 1976).

No information was available on the quantities of isopropyl oils formed per kg of isopropyl alcohol produced by either process.

(b) Use

No evidence has been found that isopropyl oils have ever been used commercially.

## 2.2 Occurrence

### Isopropyl alcohol

Isopropyl alcohol has been detected in air samples from polypropylene production plants at concentrations of up to 340 mg/m$^3$ (Shvedchenko, 1969), and as 2.7% of the total gaseous emission from streptomycin production (Kondakova et al., 1973).

It has been detected in trace quantities in some samples of drinking-water in the US (US Environmental Protection Agency, 1975) and as a constituent of tar-water resulting from the distillation of shale tar (Eizen et al., 1966).

Isopropyl alcohol has been detected in the volatiles of the following products: grapefruit essence oil (Coleman et al., 1972), roasted filbert nuts (Kinlin et al., 1972), lime essence (Moshonas & Shaw, 1972), Reunion geranium oil (Pelargonium roseum Bourban) (Timmer et al., 1971), Pinus densiflora logs (Oda, 1974) and milk products (Palo & Ilkova, 1970).

### Isopropyl oils

Isopropyl oils are not known to occur naturally; they are found only as a by-product in factories manufacturing isopropyl alcohol.

## 2.3 Analysis

### Isopropyl alcohol

A review of methods for sampling and analysing isopropyl alcohol in air has been published (NIOSH, 1976).

The Association of Official Analytical Chemists (AOAC) has published an Official Final Action for the determination of isopropyl alcohol in a variety of flavour extracts, using a titrimetric method in the absence of acetone and a colorimetric method if acetone is present. The AOAC has also published official methods for determining isopropyl alcohol in drugs and flavours by gas chromatography using a flame ionization detector (Horwitz, 1975). The gas chromatographic method for drugs was studied collaboratively, and a standard deviation of 0.142-1.079 was found among 9 laboratories (Falcone, 1973).

The majority of methods for determing isopropyl alcohol use gas chromatography with flame ionization detection. In the determination of residual isopropyl alcohol in oilseed meals and flours, there is a simple volatilization procedure for preparing samples for gas chromatography (Fore et al., 1971). Head-space analysis using gas chromatography has been employed for its determination in cosmetics at concentrations of more than 0.5% (Grant, 1974). Concentrations of more than 10 mg/l have been determined in blood by direct injection into the gas chromatograph (Jain, 1971), and 0.2 mg/l has been found in milk and milk products by direct injection onto porous polymer bead columns (Palo & Ilkova, 1970). Direct injection into gas chromatographs using flame ionization detection has been used for the analysis of environmental pollutants, including isopropyl alcohol, with a sensitivity of 0.2 µg/l (Dmitriev & Kitrosskii, 1969). Gas chromatography has also been used for the analysis of fruits dewaxed with isopropyl alcohol (Calhoun & Dellamonica, 1974).

Concentrations of 505-1890 mg/m$^3$ in the working atmosphere have been determined by gas chromatography (NIOSH, 1976), and the limit of detection of gas chromatographic-mass spectrometric analysis of the ambient air was 20 ppm (49 mg/m$^3$) (Cooper et al., 1971).

Infra-red spectrophotometry of the ester formed by reaction with nitrous acid has been used to determine as little as 4 µl isopropyl alcohol in foods (Coppini & Albasini, 1969).

Isopropyl oils

Isopropyl oils formed as by-products of the indirect hydration (strong-acid) process have also been analysed by mass spectroscopy combined with chromatography (Weil et al., 1952).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Isopropyl alcohol has been inadequately tested in mice by skin application, inhalation exposure and subcutaneous injection. Due to various limitations of these studies, no evaluation of the carcinogenicity of this compound can be made.

Isopropyl oils formed during the strong-acid process for synthesis of isopropyl alcohol were tested in mice by skin application, inhalation exposure and subcutaneous injection, and isopropyl oils formed during the weak-acid process were tested in mice by skin application and subcutaneous injection. Although an increased incidence of lung tumours was observed following inhalation or subcutaneous injection of isopropyl oils formed during the strong-acid process, all of these studies had some limitations due to short duration or incomplete reporting and to the unknown or variable composition of the materials tested. The available data thus do not provide sufficient evidence on which to base an evaluation of the carcinogenicity of isopropyl oils in experimental animals.

### 4.2 Human data

In two factories manufacturing isopropyl alcohol by the strong-acid process, involving the formation of isopropyl oils as by-products, an excess risk of cancers of the paranasal sinuses was found. An excess risk of laryngeal cancer may also have been present.

# Melphalan

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. Reg. Serial No.: 531-76-0*

Chem. Abstr. Name: 4-[Bis(2-chloroethyl)amino]-DL-phenyl]alanine
3-{para-[Bis(2-chloroethyl)amino]phenyl alanine; DL-3-{para-[bis-(2-chloroethyl)amino]phenyl}alanine; CB-3307; para-di(2-chloroethyl)-amino-DL-phenylalanine; merfalan; NSC-14210; phenylalanine mustard**; DL-phenylalanine mustard; sarcolysin**; DL-sarcolysin; sarcolysine**; DL-sarcolysine

Sarcoclorin

### 1.2 Chemical formula and molecular weight

See melphalan.

### 1.3 Chemical and physical properties of the pure substance

(a) Description: Needles from methanol

(b) Melting-point: 180-181°C (decomposition)

(c) Optical rotation: Optically inactive

### 1.4 Technical products and impurities

Although it is believed to be marketed in the USSR, no data were available.

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* Merphalan was originally allocated the Chem. Abstr. Reg. Serial No. 51-87-6; this has now been deleted, and the correct number is 531-76-0.

** This name is also used for melphalan, the L-isomeric constituent of merphalan, a DL-racemic mixture.

## 2. Production, Use, Occurrence and Analysis

### 2.1 Production and use

Merphalan was synthesized in the UK according to the method described for melphalan. At the same time, workers in the USSR synthesized merphalan by treating acetamido-para-aminobenzylmalonic ester with ethylene oxide and then with thionyl chloride to give acetamido-para-di(2-chloroethyl)amino-benzylmalonic ester, which was converted to merphalan by prolonged heating with hydrochloric acid (Larionov et al., 1955).

Merphalan has been tested clinically as an antineoplastic agent in Europe and Japan (White, 1960) and is used as such in the USSR.

### 2.2 Occurrence

Merphalan is not known to occur in nature.



### 2.3 Analysis

The three stereoisomers react similarly with 4(4'-nitrobenzyl)-pyridine; this can be used for their determination in plasma and urine and is sensitive down to 5 µg/ml (Truhaut et al., 1963). The method has been used to follow the reaction of phenylalanine mustards with blood in vivo and in vitro (Katz et al., 1960). Reactions with 2-nitroindan-1,2-dione (Kozlov & Bernshtein, 1968, 1970), sodium tetraphenylborane (De Carnevale-Bonino et al., 1971) and para-N,N-dimethylaminobenzaldehyde (Kozlov & Bernshtein, 1968) have also been used to determine phenylalanine mustards. UV-spectrophotometry (Belousova, 1961), spectrofluorometry (detection limit, 0.05 µg/ml) (Chirigos & Mead, 1964) and titrimetry (British Pharmacopoeia Commission, 1973) can be used to determine the pure compounds in aqueous solution.

Phenylalanine mustards and their hydrolysis products have been separated by gas-liquid chromatography of the trimethylsilyl derivatives (Goras et al., 1970) and by two-dimensional thin-layer chromatography on Kieselgel G (Valthier & Jemey, 1968).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Melphalan is carcinogenic in mice and rats following its intraperitoneal injection, producing lymphosarcomas and a dose-related increase in lung tumours in mice and peritoneal sarcomas in rats. Merphalan (a mixture of medphalan and melphalan) produced an increased incidence of mammary fibroadenomas in rats following its intraperitoneal injection in single doses.

### 4.2 Human data

The available case reports suggest that the incidence of acute leukemia is increased in myeloma patients treated with melphalan.

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

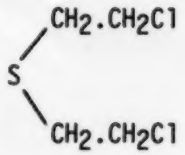
Chem. Abstr. Reg. Serial No.: 505-60-2

Chem. Abstr. Name: 1,1'-Thiobis(2-chloroethane)

Bis(2-chloroethyl)sulphide; bis(β-chloroethyl)sulphide; 1-chloro-2-(β-chloroethylthio)ethane; 2,2'-dichlorodiethyl sulphide; di-2-chloroethyl sulphide; β,β'-dichloroethyl sulphide; Schwefel-Lost; S-lost; S mustard; sulphur mustard; sulphur mustard gas; yellow cross liquid

Yperite

### 1.2 Chemical formula and molecular weight



$C_4H_8Cl_2S$ Mol. wt: 159.1

### 1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless, odourless, oily liquid; forms prisms on cooling

(b) Melting-point: 13-14°C

(c) Boiling-point: 215-217°C at 760 mm Hg; 108°C at 14 mm Hg; 98°C at 10 mm Hg

(d) Density: $d_4^{20}$ 1.274 (liquid); $d^{13}$ 1.338 (solid)

(e) Refractive index: $n_D^{20}$ 1.531

(f) Solubility: Sparingly soluble in water (0.68 g/l at 25°C); soluble in fat, fat solvents and other common organic solvents (Seidell, 1941; Stecher, 1968)

(g) Volatility: Volatile with steam; vapour pressure at 0°C is 0.025 mm Hg, and 0.09 mm Hg at 30°C

(h) Stability: Hydrolysed in aqueous solution (t1/2, 5 minutes at 37°C). The products of hydrolysis are thiodiglycol and hydrochloric acid (Berenblum, 1935).

(i) Reactivity: Reacts with sulphydryl and imidazole groups (Dawson et al., 1959). Its reaction with bleach and chlorine provides a method of decontamination.

## 1.4 Technical products and impurities

Mustard gas is believed to be produced in small quantities by manufacturers of laboratory chemicals.

## 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p.17.

## 2.1 Production and use

Mustard gas may have been synthesized by Despretz (Despretz, 1822), but large quantities were not manufactured until World War I: by 1919, US production had increased to approximately 18,000 kg per day. At that time mustard gas was synthesized in the US by reacting ethylene with sulphur monochloride at 30-35°C. In Germany it was produced by treating ethylene first with hypochlorous acid and then with sodium sulphide, to yield $\beta,\beta'$-dihydroxyethyl sulphide. This product was then heated with hydrochloric acid, yielding mustard gas (Jackson, 1936).

Mustard gas was used as a vesicant in chemical warfare during World War I and in Ethiopia in 1936 (United Nations, 1969). Although no further military use was reported, production and stockpiling of this chemical continued, especially during World War II (Rose, 1968) and stocks may still have existed in the US as recently as 1974 (Anon., 1974).

Mustard gas has been tested as an antineoplastic agent (Huntress et al., 1963); but its clinical use as a tumour inhibitor has been minimal. It is used as a model compound in biological studies on alkylating agents.

## 2.2 Occurrence

For some time after July 1917, much of the French soil in the region of battle lines was contaminated with mustard gas (Case & Lea, 1955). The average and maximum atmospheric concentrations likely to have been produced under military conditions, in the area of falling shells, have been estimated to be 3 and 5 ppm respectively (Thorpe, 1974).

## 2.3 Analysis

Gas chromatographic methods are available for the determination of mustard gas (Albro & Fishbein, 1970; Casselmann et al., 1973). It can also be estimated in air at levels of 0.5-1 µg/l air using detection tubes containing 4-(4'-nitrobenzyl)pyridine complexes with bivalent mercury, nickel and magnesium salts and using purified activated silica gel as carrier (Kratochvil & Martinek, 1969).

# 4. Comments on Data Reported and Evaluation

## 4.1 Animal data

Mustard gas is carcinogenic in mice, the only species tested, following their exposure to its vapours or following its intravenous injection, inducing an increase in the incidence of lung tumours. Following its subcutaneous injection in mice, it produced a low incidence of sarcomas at the site of injection.

## 4.2 Human data

There is evidence of an increased incidence of cancers of the respiratory tract in men exposed to mustard gas.

# 2-Naphthylamine*

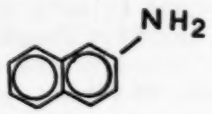
## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. No.: 91-59-8

2-Aminonaphthalene; beta-naphthylamine; BNA; Fast Scarlet Base B

### 1.2 Chemical formula and molecular weight




$C_{10}H_9N$ Mol. wt: 143.2

### 1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless crystals which darken in air to a reddish-purple colour

(b) Boiling-point: 306°C (158°C at 10 mm)

(c) Melting-point: 111-113°C

(d) Solubility: Soluble in hot water, alcohol, ether and many other organic solvents

(e) Stability: Stable in cold in the absence of air; oxidizes in the presence of air

(f) Volatility: Volatile in steam

(g) Chemical reactivity: A weak base; has the general characteristics of primary aromatic amines

### 1.4 Technical products and impurities

The commercial product contains a number of polyaromatic heterocyclic compounds including 3,4,5,6-dibenzophenazine, which

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* Considered by the Working Group in Lyon, June 1973.

is formed from 2-naphthylamine in the presence of air. 2-Amino-1,4-naphthoquinone-$N^4$, 2-naphthylimine has also been reported as a contaminant of 2-naphthylamine (Radomski et al., 1971).

## 2. Production, Use, Occurrence and Analysis

### (a) Production and use[1]

2-Naphthylamine has been produced commercially for at least 50 years (US Tariff Commission, 1922). The usual method of commercial manufacture is believed to have been the reaction of 2-naphthol with ammonia and ammonium sulphite.

Data for United States production in 1955 (the latest available) indicate that a total of 581 thousand kg were produced by four manufacturers (US Tariff Commission, 1956). Commercial production of 2-naphthylamine reportedly continued in the US until early 1972 (Hyatt, 1973), but production in recent years is believed to have been quite small.

US imports through the principal customs districts were last of significance in 1967 when they amounted to 17.4 thousand kg (US Tariff Commission, September 1968).

Data on production of 2-naphthylamine in countries other than the US were not available. The United Kingdom and several other countries reportedly discontinued production prior to 1960 because of evidence of bladder cancer resulting from exposure to the chemical (Kilner & Samuel, 1960). In 1969, the Federal Republic of Germany was reported to have had one producer of "naphthylamine and derivatives" (not further specified) in 1967; and Japan was reported in 1972 to have three producers.

The major use for 2-naphthylamine appears to have been as an intermediate in the manufacture of dyes and antioxidants.

2-Naphthylamine can be used as an intermediate in the production of twenty-one dyes. However, it is not now usually used as such, and frequently 2-amino-1-naphthalene-sulphonic acid is substituted for it (The Society of Dyers and Colourists, 1971).

At one time 2-naphthylamine was the preferred intermediate for the manufacture of J-acid (2-amino-5-naphthol-7-sulphonic

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[1] Data from Chemical Information Services, Stanford Research Institute, USA.

acid) and gamma-acid (7-amino-1-naphthol-3-sulphonic acid), but these two dye intermediates are now made by alternative methods (Kilner & Samuel, 1960). It is believed that 2-naphthylamine was used until recent years in the synthesis of N-alkyl-2-naphthylamines (e.g., N-ethyl-2-naphthylamine), which found use as dye intermediates.

Although the antioxidant N-phenyl-2-naphthylamine and another antioxidant derived from it, N-phenyl-2-naphthylamine-acetone condensate, may have been made from 2-naphthylamine in the US in the past, it is probable that these products have been manufactured by the condensation of aniline with 2-naphthol in recent years. N-Phenyl-2-naphthylamine is known to be produced in countries other than the US, but the method of synthesis is not known.

(b) Occurrence

2-Naphthylamine has not been reported to occur as such in nature. However, it is formed in the pyrolysis of nitrogen-containing organic matter. For example, the pyrolysis of L-glutamic acid and L-leucine at 700°C (but not at 500°C) may produce 1- and 2-naphthylamine (Masuda et al., 1967). 2-Naphthylamine reportedly has been found in coal-tar (Treibl, 1967); gas retort houses have been shown to have atmospheric levels of 2-naphthylamine sufficient to give a human exposure of 0.2 µg per day (Battye, 1966). Cigarette smoke contains 0.02 µg of 2-naphthylamine per cigarette, which is equivalent to 1 µg per 50 cigarettes, the daily exposure of a heavy cigarette smoker (Hoffmann et al., 1969).

2-Naphthylamine is present as an impurity in commercial 1-naphthylamine. The specifications for US-produced 1-naphthylamine indicate that the content is at present 0.5% or less. Other commercial 1-naphthylamine may contain higher percentages. 2-Naphthylamine may occur in the waste streams from plants where it is produced and used; it has been reported to be present in the effluent from certain dyestuffs factories in Japan (Takemura et al., 1965).

The presence, use and manufacture of $\beta$-naphthylamine in factories is prohibited in the UK under the Carcinogenic Substances Regulations 1967 - Statutory Instrument (1967) No. 487. It is also listed with 13 other compounds in the US Federal Register (US Government, 1973) as subject to an emergency temporary standard on certain carcinogens under an order made by the Occupational Safety and Health Administration, Department of Labor, on 26 April, 1973.

(c) Analysis

Guidelines for the analysis of aromatic amines are available (UICC, 1970).

Methods to determine relatively gross amounts of 2-naphthylamine in the presence of other industrial aromatic amines have been described (Butt & Strafford, 1956). A colorimetric determination of the oxidation products obtained from 2-naphthylamine and a large number of other aromatic amines has been published (Gupta & Srivastava, 1971).

2-Naphthylamine can be separated from other non-volatile aromatic amines by thin-layer chromatography (Sawicki et al., 1966). Separation from 1-naphthylamine can also be achieved by thin-layer chromatography (Shimomura & Walton, 1968; Ghetti et al., 1968). A gas chromatographic method in which 1- and 2-naphthylamine are separated after reaction with pentafluoropropionic anhydride will detect levels down to 1 ng (Masuda & Hoffmann, 1969).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

2-Naphthylamine is carcinogenic in the mouse, hamster, dog and monkey. Given orally it has produced bladder carcinomas in the dog and monkey, and, at high dosage levels, in the hamster. By this route, it has increased the incidence of hepatomas in the mouse; in the rat and rabbit, it has little, if any, carcinogenic effect.

### 4.2 Human data

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or when present as an impurity in other compounds, is strongly associated with the occurrence of bladder cancer. There is no doubt that 2-naphthylamine is a human bladder carcinogen.

# Nickel and Nickel Compounds*

## 1. Chemical and Physical Data

Nickel and nickel compounds were first considered by an IARC Working Group in 1972 (IARC, 1973). Since that time new data have become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

## 1. Chemical and Physical Data

### 1.1 Synonyms and formulae

Table I

(Chemical Abstracts names are underlined.)

| Chemical Name | Chem. Abstr. Reg. Serial No. | Synonyms | Formula |
|---|---|---|---|
| Nickel | 7440-02-0 | Carbonyl nickel powder; C.I. No. 77775 | |
| Nickel acetate | 373-02-4 | Acetic acid, nickel (2+) salt; nickel (II) acetate; nickelous acetate | $Ni(COOCH_3)_2$ |
| Nickel acetate tetrahydrate | 6018-89-9 | Acetic acid, nickel (2+) salt, tetrahydrate; nickel (II) acetate tetrahydrate nickelous acetate tetrahydrate | $Ni(COOCH_3)_2 .4H_2O$ |
| Nickel ammonium sulphate | 15699-18-0 | Sulphuric acid, ammonium nickel (2+) (2:2:1) | $Ni(NH_4)_2 (SO_4)_2$ |

* Considered by the Working Group, December 1975

| | | | |
|---|---|---|---|
| Nickel ammonium sulphate (cont'd) | 51287-85-5 | Sulphuric acid, ammonium nickel (2+) (1:2:1) | $Ni(NH_4)_2SO_4$ |
| | 25749-08-0 | Sulphuric acid, ammonium nickel (2+) (3:2:2) | $Ni_2(NH_4)_2(SO_4)_3$ |
| Nickel carbonate | 3333-67-3 | Carbonic acid, nickel (2+) salt; C.I. No. 77779; nickel (II) carbonate; nickelous carbonate | $NiCO_3$ |
| Nickel carbonate, basic | 39380-74-0 | Nickel (2+) salt (1:1), mixture with nickel hydroxide [Ni(CH)2] hydrate | $2NiCO_3.3Ni(OH)_2.4H_2O$ |
| | 1271-28-9 | Zaratite | $NiCO_3.2Ni(OH)_2.4H_2O$ |
| Nickel carbonyl | 13463-39-3 | Nickel tetracarbonyl | $Ni(CO)_4$ |
| Nickel chloride | 7718-54-9 | Nickel(II) chloride; nickel dichloride; nickelous chloride | $NiCl_2$ |
| Nickel fluoborate | 15684-36-3 | Borate (1-) tetrafluoro-nickel (2+); fluoboric acid, nickel (II) salt | $Ni(BF_4)_2.6H_2O$ |
| Nickel fluoride | 10028-18-9 | Nickel difluoride; nickel (II) fluoride nickelous fluoride | $NiF_2$ |
| Nickel hydroxide | 12054-48-7 | Nickel (II) hydroxide; Nickelous hydroxide | $Ni(OH)_2$ |
| | 12125-56-3 | Nickel (III) hydroxide | $Ni(OH)_3$ |
| | | Nickelic hydroxide | $NiO.nH_2O$ |
| Nickel iron sulphide | 53809-87-3 | Iron nickel sulphide; violarite | $Ni_2FeS_4$ |
| Nickel monosulphide | 16812-54-7 | Nickel sulphide[1] | NiS |

[1] This name is also used for nickel subsulphide; there is considerable confusion in the published literature between these two substances and other nickel sulphides (e.g., $Ni_4S_3$, $Ni_2S$, $NiS_2$).

| | | | |
|---|---|---|---|
| Nickel nitrate | 21659-66-5 | Nickel (II) nitrate; nickelous nitrate; nitric acid, nickel (2+) salt | $Ni(NO_3)_2$ |
| Nickelocene | 1271-28-9 | Bis($\eta^5$-2,4-cyclopentadien-1-yl) nickel; di-$\pi$-cyclopentadienyl-nickel | $(C_5H_5)_2Ni$ |
| Nickel oxide | 1213-99-1 | Green nickel oxide; nickel monoxide; nickelous oxide nickel (II) oxide; nickel protoxide | NiO |
| | 1314-06-3 | Black nickel oxide; nickelic oxide; nickel (III) oxide; nickel sesquioxide; nickel trioxide | $Ni_2O_3$ |
| Nickel subsulphide | 12035-72-2 | Heazlewoodite; nickel sulphide[1] | $Ni_3S_2$ |
| Nickel sulphamate | 13770-89-3 | Nickel (II) sulphamate; sulphamic acid, nickel (2+) salt (2:1) | $Ni(SO_3NH_2)_2$ |
| Nickel sulphate | 7786-81-4 | Nickelous sulphate; nickel (II) sulphate; sulphuric acid, nickel (2+) salt | $NiSO_4$ |

## 1.2 Chemical and physical properties

Physical properties of the nickel compounds considered in this monograph are given, when available, in Table II. Additional information on solubility is given below.

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1 This name is also used for nickel monosulphide; there is considerable confusion in the published literature between these two substances and other nickel sulphides (e.g., $Ni_4S_3$, $Ni_2S$, $NiS_2$).

## Table II[a]

| Chemical name | Atomic/mol. weight | Melting-point °C | Boiling point °C | Crystal system | Density g/cm$^3$ |
|---|---|---|---|---|---|
| Nickel | 58.71 | 1453 | 2732 | face-centre cube[d] | 8.90 |
| Nickel acetate | 176.80 | dec. | 16.6 | prism | 1.798 |
| Nickel ammonium sulphate[b] | 395 | | | monoclinic | 1.923[d] |
| Nickel carbonate, basic[c] | 376.24 | | | cubic | |
| Nickel carbonyl | 170.75 | -25 | 43 | liquid | 1.32 (17°C) |
| Nickel chloride | 129.62 | 1001 | 973 (subl.) | | 3.55 |
| Nickel fluoborate[b] | 232.31 | dec. | | | |
| Nickel fluoride | 96.71 | 1000 (subl.)(in HF) | | tetragonal[a,c] | 4.63[a,c] |
| Nickel hydroxide | 92.72 | 230 (dec.) | | | 4.15 |
| Nickel iron sulphide | 301.27 | | | isometric | |
| Nickel monosulphide | 90.77 | 797 | | trigonal | 5.3-5.65 |
| Nickel nitrate[b] | 290.81 | 56.7 | 136.7 | monoclinic deliquescent | 2.05 |
| Nickelocene | 188.90 | | 130 (subl.) | | |
| Nickel oxide NiO | 74.71 | 1990 | | cubic | 6.67 |
| $Ni_2O_3$ | 165.42 | 600 (dec.)[d] | | | |
| | | | | | 5.82 |
| Nickel subsulphide | 240.26 | 790 | | | |
| Nickel sulphamate | 252.90 | 500 (dec.) | | | |
| Nickel sulphate | 154.78 | 848 (dec.) | | cubic | 3.68 |

a Data from Weast (1975) unless otherwise specified

b As the hexahydrate

c Haendler et al. (1952)

d Stecher (1968)

e Zaratite

Nickel metal - soluble in dilute nitric acid and slightly soluble in hydrochloric and sulphuric acids (Weast, 1975). The solubility of metallic nickel in tissue and body fluids has been discussed by Weinzierl & Webb (1972).

Nickel acetate - soluble in acetic acid (12.4 mol. % at 30°C) (Stephen & Stephen, 1963).

Nickel ammonium sulphate - soluble in water (6.10 wt % at 20°C) (Stephen & Stephen, 1963); insoluble in ethanol

Nickel carbonate, basic - insoluble in water, soluble in hot dilute hydrochloric acid and ammonium hydroxide (Weast, 1975)

Nickel carbonyl - very slightly miscible with water (0.016 g/100 ml at 9.8°C) (Weast, 1975); miscible with ethanol, benzene, chloroform, acetone and carbon tetrachloride

Nickel chloride - soluble in water (64.2 g/100 ml at 20°C and 87.6 g/100 ml at 100°C) (Weast, 1975); soluble in ethylene glycol (16.2 wt % at 20°C), ethanol (9.13 wt % at 20°C) and hydrazine (0.8 g/100ml at 20°C) (Stephen & Stephen, 1963)

Nickel fluoborate - very soluble in water and 95% ethanol; also soluble in ethanol/ether mixtures (Stacey et al., 1960)

Nickel fluoride - slightly soluble in water (4 g/100 ml at 25°C) (Emeleus, 1950); soluble in acids, alkalis and ammonia (Weast, 1975)

Nickel hydroxide - soluble in aqueous ammonia; practically insoluble in water (0.00127 g/100 ml at 20°C) (Stephen & Stephen, 1963)

Nickel monosulphide - very slightly soluble in water (0.4 mg/100 ml at 18°C) (Weast, 1975)

Nickel nitrate - soluble in water (48.5 wt % at 20°C), in hydrazine (3 g/100 ml at 20°C) and in ethylene glycol (7.5 wt % at 20°C) (Stephen & Stephen, 1963)

Nickelocene - soluble in common organic solvents (Paulson, 1955)

Nickel oxide - nickel oxide (NiO) is practically insoluble in water (0.11 mg/100 ml at 20°C) (Blaszkiewicz, 1967). Nickel oxide ($Ni_2O_3$) is insoluble in water, very slightly soluble in cold acid, soluble in hot hydrochloric acid (with the evolution of chlorine) and soluble in hot sulphuric or nitric acid (with the evolution of oxygen) (Stecher, 1968).

Nickel subsulphide - insoluble in water and soluble in nitric acid (Weast, 1975). Its solubility in serum and in serum ultrafiltrate has been discussed by Sunderman et al. (1976).

Nickel sulphamate - soluble in water (Santmyers & Aarons, 1967)

Nickel sulphate - very soluble in water (27.3-27.7 wt % at 20°C); soluble in methanol (0.11 wt % at 35°C) and ethanol (0.02 wt % at 35°C) (Stephen & Stephen, 1963)

## 1.3 Technical products and impurities

Specifications from manufacturers indicate that impurities in nickel salts generally include some zinc, copper and iron. Typical compositions of nickel compounds and nickel metal have been described by Dean (1959)

## 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p.19.

Two reviews on nickel metal and alloys are available (Adamec & Kihlgren, 1967; Broache, 1970). A review of the chemistry of nickelocene is given by Barnett (1974).

## 2.1 Production and use

World mine production of nickel in 1971 was about 640 million kg, and in 1973 preliminary figures showed it to be about 660 million kg (Corrick, 1973). Table III gives the world production by country for 1973.

US demand for nickel increased from about 160 million kg in 1964 to 235 million kg in 1973 (US Bureau of Mines, 1975). In that year, nickel was used as follows: transportation, 20.9%; chemicals, 14.9%; electrical goods, 12.9 ; fabricated metal products, 10%; miscellaneous uses, 9.7%; petroleum, 8.9%; construction, 8.9%; machinery, 6.9%; household appliances, 6.9% (US Bureau of Mines, 1975).

Nickel metal Nickel ingots and pellets are produced commercially by the electrolytic and Mond carboyl processes. Its principal use is as an alloying additive in steel manufacture; it is also used in the production of coins, domestic utensils, monel metals and other alloys.

Table III

World mine production of nickel[a] by country (Corrick, 1973)

| Country[b] | Million kg |
|---|---|
| Australia (content of concentrate) | 40 |
| Brazil (content of ore) | ≈3.1 |
| Burma (content of speiss) | ≈0.03 |
| Canada[c] | 243 |
| Cuba (content of oxide and sulphide) | ≈31 |
| Dominican Republic | ≈24 |
| Finland (content of concentrate | 5.8 |
| " ( " " nickel sulphate) | ≈0.2 |
| Greece (recoverable content of ore) | 12.6 |
| Indonesia (content of ore)[d] | 20.8 |
| Morocco (content of nickel and cobalt ore) | ≈0.3 |
| New Caledonia (recoverable)[e] | 99 |
| Norway (content of concentrate) | ≈0.4 |
| Poland (content of ore) | ≈2 |
| Republic of South Africa | ≈10.4 |
| Rhodesia (content of concentrate | ≈12 |
| United States (content of ore shipped) | 16.6 |
| USSR (content of ore) | ≈136 |
| Total | 658 |

a As far as possible, this table represents mine production of nickel; where data relate to some more highly processed form, figures have been given to provide some indication of the magnitude of mine output; where only an estimate was available, this is indicated.

b In addition to the countries listed, Albania and the German Democratic Republic mine nickel, but available information is inadequate for reliable estimates of output levels to be made.

c Refined nickel and nickel content of oxides and salts produced, plus recoverable nickel in exported mattes and speiss

d Includes a small amount of cobalt not recovered separately

e Nickel-colbalt content of metallurgical plant products, plus recoverable nickel-cobalt in exported ores

Nickel powder is produced commercially by the Mond process and its variations: nickel or nickel ore is reacted with carbon monoxide to produce nickel carbonyl gas, which is then decomposed by heat to give pure, finely divided nickel. In another method of production, the nickel and cobalt contents of nickel oxide ores are recovered as carbonates, which are calcined to nickel oxide and reduced to nickel powder.

Many of the products made from nickel metal are also manufactured from finely divided nickel powder. It is also used as a hydrogenation catalyst.

Nickel acetate is produced commercially by reacting sodium acetate with a nickel sulphate solution. US consumption of all organic nickel salts in 1968 was estimated to be 227 thousand kg, almost all of which was nickel acetate.

It is used mainly as a mordant in the textile industry and to a minor extent as a hydrogenation catalyst.

Nickel ammonium sulphate is prepared by reacting nickel sulphate with ammonium sulphate (McMurdie et al., 1971). It is used in electroplating, but to a lesser extent than is nickel sulphate (Antonsen & Springer, 1967).

Nickel carbonate Only basic nickel carbonate ($2NiCO_3 . 3Ni(OH)_2 . 4H_2O$) is produced commercially. It is largely produced and consumed during the manufacturing of nickel oxide, nickel powder and nickel catalysts. Canada is the largest single producer of this material.

It has been estimated that 908 thousand kg of nickel salts other than nickel sulphate were consumed in the US in 1970; nickel carbonate probably accounted for most of these.

US consumption of basic nickel carbonate is largely in the production of nickel catalysts for use in organic chemical manufacture, petroleum refining and edible oil hardening. A high purity basic nickel carbonate is used in electronic components such as ferrites and thermistors. The total amount of nickel carbonate thus consumed is minor, but the number of individuals exposed could be quite high because of the large number of electronic component companies making and using ferrites and thermistors.

Nickel carbonyl is produced by the Mond process and its variations, as described above for nickel powder. Total annual production is estimated to be less than 6.8 million kg.

On a worldwide basis, the major uses of nickel carbonyl are as an intermediate product in the refining of nickel, in the manufacture of high purity nickel powder for powder metallurgy, in the fabrication of nickel and nickel alloy components and shapes and in the manufacture of catalysts. For these uses the carbonyl is contained within process equipment, with provisions to minimize human exposure in case of equipment failures. However, the facility with which it is made and converted into nickel has resulted in a large number of small-scale uses for the carbonyl, where exposure of personnel and venting to the atmosphere may constitute a hazard (e.g., vapour plating of nickel and depositing of nickel in semiconductor manufacture).

Nickel chloride may be prepared from nickel oxide by chlorination or by reaction with hydrogen chloride (Antonsen & Springer, 1967). It is one of the principal nickel compounds used in electroplating (Antonsen & Springer, 1967).

Nickel fluoborate has been prepared from aqueous solution as the hexahydrate; it cannot be dehydrated without decomposition (Stacey et al., 1960), and it is used as an electrolyte in high-speed plating (Antonsen & Springer, 1967).

Nickel fluoride may be prepared by the reaction of fluorine on finely divided nickel powder (Haendler et al., 1952), by the reaction of anhydrous nickel chloride with fluorine or hydrogen fluoride, or by the fusion of nickel chloride with ammonium fluoride (Emeleus, 1950).

Nickel fluoride is used in battery cathodes (Cogley et al., 1973).

Nickel hydroxide may be prepared from solutions of nickel salts by precipitation with alkaline hydroxides, but the product is usually contaminated by occluded or absorbed foreign salts. Pure nickel hydroxide can be prepared by electrolytic precipitation using nickel anodes (Antonsen & Springer, 1967).

It is used as a catalyst and in nickel-cadmium batteries (Antonsen & Springer, 1967).

Nickel monosulphide may be made by the direct fusion of nickel with sulphur (Antonsen & Springer, 1967); it is produced only in small quantities as a laboratory reagent.

Nickel nitrate is prepared by the reaction of nitric acid on nickel (Antonsen & Springer, 1967). It is used primarily as a catalyst and, to a lesser extent, in batteries.

Nickelocene may be prepared by the reaction of tetrapyridine nickel chloride and cyclopentadienyl sodium (Knox et al., 1961) or by a simpler method using nickel chloride, cyclopentadiene and diethylamine (Watanabe et al., 1965).

No evidence was found that nickelocene is produced in large quantities, but it is used as a laboratory reagent.

Nickel oxide is generally obtained by roasting refined nickel ores. Two partially reduced nickel oxide products, known as 'nickel oxide sinters', are produced commercially on a large scale; one contains 75% nickel and the other, 90%. Available data on nickel oxide products frequently combine information on nickel oxide powder and nickel oxide sinters.

Canada is the largest single producing country. In 1972, preliminary estimates of Canadian exports of nickel oxide were 33 million kg (Cajka, 1972). US imports of nickel oxide in 1973 (mostly from Canada) were 5.84 million kg (US Department of Commerce, 1974). In 1973, total US consumption of oxide powder and oxide sinter was reported to be 30 million kg (Corrick, 1973).

Most of the nickel oxide sinter produced is used in the manufacture of stainless and alloy steels.

Nickel subsulphide can be made by the direct fusion of nickel with sulphur (Antonsen & Springer, 1967); it is apparently not sold commercially.

Nickel sulphamate can be prepared by passing oxygen into a suspension of the powdered metal in aqueous sulphamic acid (Fischer, 1967). It is used in electroplating (Antonsen & Springer, 1967).

Nickel sulphate is produced commercially by dissolving nickel oxide in sulphuric acid and concentrating the solution to precipitate nickel sulphate heptahydrate, which on heating forms the commercial crystalline nickel sulphate hexahydrate (Antonsen & Springer, 1967).

Total US consumption in 1973 of nickel sulphate and other nickel salts was reported to be 3.3 million kg (Corrick, 1973). It is consumed as such in plating baths and also as an intermediate in the production of nickel ammonium sulphate and nickel carbonate, which are also used in nickel plating. It is used as an intermediate for depositing nickel carbonate on catalyst substrates and as the principal intermediate for the manufacture of organic nickel salts.

## 2.2 Occurrence

### Nickel

Natural environment: Over 90% of the world's nickel is obtained from pentlandite $(FeNi)_9S_8$, a mineral invariably associated with large amounts of pyrrhotite and varying amounts of chalcopyrite. Secondary nickel minerals include garnierite and annabergite (Cornwall, 1966, 1973; Fairbridge, 1974).

Air: Reviews concerning air pollution by nickel have been made by Schroeder (1970) and by the CMBEEP (1975). Increasing use of nickel enhances the probability of its appearance in the atmosphere at nickel production plants. The average concentration of nickel in air samples collected from widely scattered locations in the US in 1964 and 1965 was 340 ng/m$^3$ (Falk, 1970). It constitutes 0.03% of the particulate matter suspended in the atmosphere (Sullivan, 1969). Nickel compounds, e.g., sulphides, oxides and carbonyl, enter the atmosphere as a result of the combustion of coal, diesel oil and fuel oil (Bowen, 1966; Natusch et al., 1974).

Tobacco smoke: Traces of nickel are present in tobacco smoke (Szadkowski et al., 1969). According to Sunderman & Sunderman (1961), at the time of their report six brands of American cigarettes contained an average of between 1.59 and 3.07 µg Ni per cigarette, and 20% of this found its way into the main-stream smoke.

Water: The concentration of nickel in various water samples ranged from 3-264 µg/l (CMBEEP, 1975).

Food: Nickel levels in various foods have been summarized by the CMBEEP (1975); concentrations of up to 6.5 µg/g in cereal food-stuffs, up to 2.6 µg/g in vegetables, up to 1.7 µg/g in fish and up to 7.6 µg/g in tea were recorded.

Animal tissues: Nickel levels in animal tissues were within the range of 0-5 µg/g wet weight (Schroeder et al., 1961); levels in various human tissues are summarized by the CMBEEP (1975).

Nickel carbonate occurs in nature as the mineral zaratite, $NiCO_3.2Ni(OH)_2.4H_2O$ (Cornwall, 1966). It is formed by the decomposition of nickel carbonyl in moist air and is a potential atmospheric and surface water pollutant.

Nickel carbonyl In addition to its use as a synthetic intermediate in plants producing nickel and nickel products, nickel carbonyl may be present wherever carbon monoxide contacts nickel and nickel alloys.

Nickel iron sulphide is found in nature as the mineral violarite, $Ni_2FeS_4$ (Cornwall, 1966). It is a secondary mineral formed from primary sulphides in the weathering zone by circulating ground water.

Nickel oxide The principal natural form of nickel oxide occurs in a mixture with nickel sulphides in varying proportions in weathered ore. It is formed by the decomposition of nickel carbonyl in dry air.

Nickel subsulphide is found in nature as the mineral heazlewoodite, $Ni_3S_2$. It is not believed to be a significant atmospheric or water pollutant.

Nickel sulphate occurs as a minor mineral, morenosite, $NiSO_4.7H_2O$ (Cornwall, 1966), formed in the weathering of primary nickel minerals. Because of its widespread use in plating baths, nickel sulphate may appear as a water pollutant in industrial areas where such baths are discarded or their parts washed after the plating operation.

## 2.3 Analysis

Several reviews on the analysis of elemental nickel have been published (CMBEEP, 1975; Lewis & Ott, 1970; Peshkova & Savostina, 1971). Atomic absorption spectrophotometry is one of the principal methods of analysis used for nickel in both air and water (Sachdev & West, 1970). The dimethylglyoxine method for colorimetric determination of traces of nickel was outlined by Sandell (1959). Gas chromatography has been used for the detection of nickel carbonyl in blood and breath (Sunderman et al., 1968).

# 4. Comments on Data Reported and Evaluation

## 4.1 Animal data

Nickel subsulphide is carcinogenic in rats following its inhalation: it produced malignant lung tumours. Intramuscular injection and/or implantation of nickel subsulphide, nickel powder, nickelocene or nickel oxide, carbonate or hydroxide produced local rhabdomyosarcomas and/or fibrosarcomas in rats; nickel subsulphide and nickel oxide produced similar tumours in mice and nickel powder and nickelocene, in hamsters. A dose-response relationship for local tumour induction after intramuscular injection of nickel subsulphide has been demonstrated in rats.

Administration of nickel carbonyl to rats by repeated intravenous injection was associated with an increased incidence of malignant tumours in various tissues. Inhalation exposure of rats to nickel carbonyl was associated with a few pulmonary malignancies.

## 4.2 Human data

Epidemiological studies conclusively demonstrate an excess risk of cancer of the nasal cavity and lung in workers in nickel refineries. It is likely that nickel in some form(s) is carcinogenic to man.

# Oxymetholone

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

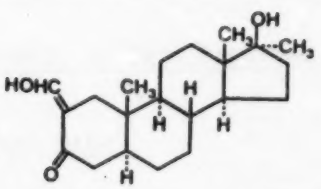
Chem. Abstr. Reg. Serial No.: 434-07-1

Chem. Abstr. Name: 17-Hydroxy-2-(hydroxymethylene)-17-methyl-5α,17β-androstan-3-one

4,5-Dihydro-2-hydroxymethylene-17α-methyltestosterone; HMD; 17β-hydroxy-2-hydroxymethylene-17α-methyl-3-androstanone; 17β-hydroxy-2-(hydroxymethylene)-17α-methyl-5α-androstan-3-one; 17-hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one; 2-hydroxymethylene-17α-methyl-5α-androstan-17β-ol-3-one; 2-hydroxymethylene-17α-methyl-dihydrotestosterone; 2-(hydroxymethylene)-17-methyldihydrotestosterone; 2-(hydroxymethylene)-17α-methyldihydrotestosterone; 2-hydroxymethylene-17α-methyl-17β-hydroxy-3-androstanone; 17α-methyl-2-hydroxymethylene-17-hydroxy-5α-androstan-3-one; oximetholonum; oximetolona; oxymethenolone

Adroidin; Adroyd; Anadrol; Anadroyd; Anapolon; Anasteron; Anasteronal; Anasterone; Becorel; CI-406; Dynasten; Methabol; Nastenon; NSC-26 198; Oxitosona-50; Pavisoid; Plenastril; Protanabol; Roboral; Synasteron; Zenalosyn

### 1.2 Chemical formula and molecular weight




$C_{21}H_{32}O_3$ Mol. wt: 332.5

### 1.3 Chemical and physical properties of the pure substance

From Weast (1975), unless otherwise specified

(a) Description: Crystals (Stecher, 1968)

(b) Melting-point: 178-180°C; 182°C

(c) Optical rotation: $[\alpha]_D^{25}$ = +36° in dioxane

(d) Spectroscopy data: $\lambda_{max}$ 285 and 315 nm ($E_1^1$ = 294 and 547) in 0.01 N methanolic sodium hydroxide[1]

(e) Solubility: Practically insoluble in water; soluble in ethanol, dioxane and ether; very soluble in chloroform (Blacow, 1972).

## 1.4 Technical products and impurities

Oxymetholone is available in the US as a National Formulary grade containing 97-103% active ingredient on a dried basis with a maximum of 3% foreign steroids or other impurities. Tablets are available in 2.5, 5, 10 and 50 mg doses that contain 90-110% of the stated amount of oxymetholone (Kastrup, 1974; National Formulary Board, 1970). In Japan, oxymetholone is also available in powder form.

# 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p.15.

## 2.1 Production and use

### (a) Production

A method of preparing oxymetholone was reported in 1959 and involved the following steps: 17α-methylandrostan-17β-ol-3-one in anhydrous thiophene-free benzene is reacted with ethyl formate and sodium hydride by stirring the mixture under nitrogen for several hours. The resulting sodium derivative is washed and then treated with cold dilute hydrochloric acid to liberate crude oxymetholone, which is purified by recrystallization from ethyl acetate (Ringold et al., 1959).

No evidence has been found that oxymetholone was ever commercially produced in the US. In 1975, two Japanese companies produced a combined total of 480 kg oxymetholone.

### (b) Use

Oxymetholone is a synthetic androgenic-anabolic steroid hormone primarily intended for use in clinical therapy to maintain a positive nitrogen balance. It can be used to reverse excess

excretion of calcium and nitrogen resulting from corticosteroid therapy, prolonged immobilization and other diseases characterized by catabolism and tissue depletion (American Society of Hospital Pharmacists, 1968). Oxymetholone is used mainly to promote weight gain to counteract weakness and emaciation resulting from debilitating diseases and after serious infections, burns, trauma or surgery. The usual adult dosage of 5 to 10 mg per day is administered orally for about 3 weeks, but not exceeding 13 weeks, for a single course of therapy. Occasionally, 30 mg per day is given (Harvey, 1975).

Oxymetholone can also be used in the treatment of anaemias caused by deficient red-cell production and in acquired and congenital aplastic anaemias, myelofibrosis and hypoplastic anaemias due to myelotoxic drugs. It can be used as an adjunct in the treatment of senile and post-menopausal osteoporosis (Kastrup, 1974).

Total US sales of oxymetholone for use in human medicine are estimated to be less than 20 kg annually. In Japan, 360 kg are estimated to have been used in 1975.

Oxymetholone has reportedly been used in veterinary medicine as an anabolic steroid for small animals (Stecher, 1968).

## 2.2 Occurrence

Oxymetholone is not known to occur in nature.

## 2.3 Analysis

A general survey of steroid analysis includes methods for anabolic steroids (Forist & Johnson, 1961). An ultraviolet spectral assay for oxymetholone in bulk and tablet form (National Formulary Board, 1970) and thin-layer chromatographic analysis (Hara & Mibe, 1967) have been described.

# 4. Comments on Data Reported and Evaluation

## 4.1 Animal data

No data were available to the Working Group.

## 4.2 Human data

Although ten cases of liver-cell tumours have been reported in patients with aplastic anaemia, Fanconi's anaemia or paroxysmal nocturnal haemoglobinuria treated for long periods with oxymetholone alone or in combination with other androgenic drugs, a causal relationship cannot be established.

The increased risk of developing liver-cell tumours could be related to hepatic damage known to be caused by oxymetholone. On the other hand, patients with congenital anaemias may have an intrinsically higher risk of developing tumours; this risk may become manifest during the extended survival resulting from administration of the drug.

# Phenacetin

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names[1]

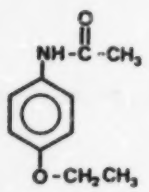
Chem. Abstr. Reg. Serial No.: 62-44-2

Chem. Abstr. Name: N-(4-Ethoxyphenyl)acetamide

para-Acetophenetide; para-acetophenetidide; acetophenetidin; acetophenetidine; para-acetophenetidine; aceto-4-phenetidine; acetophenetin; acetparaphenalide; acetphenetidin; para-acetphenetidin; acet-para-phenetidin; N-acetyl-para-phenetidine; 4'-ethoxyacetanilide; 4-ethoxyacetanilide; para-ethoxyacetanilide; para-phenacetin; phenacetine; phenacetin; phenazetin

Fenacetina; Fenedina; Fenidina; Fenina; Pertonal; Phenacet; Phenacetinum; Phenazetin; Phenedina; Phenidin; Phenin

### 1.2 Chemical formula and molecular weight




$C_{10}H_{13}NO_2$ Mol. wt: 179.2

### 1.3 Chemical and physical properties of the pure substance

From Stecher (1968), unless otherwise specified

(a) Description: Crystalline scales or powder

(b) Melting-point: 134-135°C

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[1] Only trade names of those products that contain phenacetin alone are given; there are many other products in which phenacetin is combined with other drugs.

(c) Spectroscopy data: $\lambda_{max}$ 250 nm in ethanol (US Pharmacopeial Convention, Inc., 1970); 285 nm in chloroform and isooctane (National Formulary Board, 1970).

(d) Solubility: Soluble in cold water (0.076 g/100 ml), in boiling water (1.2 g/100 ml), in ethanol (6.7 g/100 ml), in chloroform (7.1 g/100 ml), in ether (1.1 g/100 ml) and in glycerol

## 1.4 Technical products and impurities

Various national and international pharmacopoeias give specifications for the purity of phenacetin in pharmaceutical products. For example, phenacetin is available in the US as a USP grade containing 98-101% active ingredient on a dried basis and 0.03% maximum para-chloroacetanilide; it is also obtainable as tablets in 300 mg doses containing 94-106% of the stated amount (US Pharmacopeial Convention, Inc., 1970). Phenacetin is also available in the US in tablet form containing 150 mg phenacetin in combination with 230 mg aspirin and 15 or 30 mg caffeine, or with 230 mg aspirin, 30 mg caffeine and 8, 15, 30 or 60 mg codeine phosphate and containing 90-110% of the stated amount of phenacetin (National Formulary Board, 1970).

# 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p.15.

## 2.1 Production and use

### (a) Production

A method of preparing phenacetin was first reported in 1894 and involved reaction of 4-acetaminophenol with potassium ethyl sulphate in an aqueous alcoholic alkaline solution under pressure at 150°C (Prager & Jacobson, 1930). Phenacetin can also be prepared by condensing para-nitrophenol, dissolved in a sodium hydroxide solution, with ethyl bromide to give para-nitrophenetole, which is then reduced with sodium sulphide. The resulting para-phenetidine is acetylated by refluxing with acetic anhydride to give phenacetin (Swinyard, 1975).

In Japan, phenacetin is produced commercially by the pheno synthesis process , which uses the following materials: para-nitrophenol, sodium nitrate, sulphuric acid and ethyl iodide, or

by the nitration-fractional crystallization process, which uses para-chloro-nitrobenzene and mixed acid.

Phenacetin has been produced commercially in the US for over 50 years (US Tariff Commission, 1927); only one US company reported production (see preamble, p.15) in 1974 (US International Trade Commission, 1976a). The combined production of the acetanilide derivatives, phenacetin and acetaminophen, was reported to be 3,500 thousand kg in 1974 (US International Trade Commission, 1976a). US imports of phenacetin through the principal customs districts were 67,000 kg in 1972 (US Tariff Commission, 1973), 94,000 kg in 1973 (US Tariff Commission, 1974) and 192,000 kg in 1974 (US International Trade Commission, 1976b).

Phenacetin was first produced in Japan in 1935. Two companies manufactured a combined total of 276,000 kg in 1975; in that year, 40,000 kg were imported from France and less than 1,000 kg exported.

Total annual production of phenacetin in western Europe is estimated to be 1-5 million kg; the Federal Republic of Germany and France are believed to be major producing countries.

(b) Use

Phenacetin is used as an analgesic and antipyretic agent but has little anti-inflammatory activity. It is used mainly to counteract mild to moderate pain of the musculoskeletal system and is frequently combined with aspirin and caffeine. The usual dosage is 300 mg taken 4 to 6 times per day, not exceeding 2 g per day (Swinyard, 1975). Preparations containing phenacetin combined with other drugs usually contain 150 to 200 mg phenacetin (American Society of Hospital Pharmacists, 1959).

Total US sales of phenacetin for use in human medicine are estimated to be less than 640,000 kg annually.

Phenacetin is also used as a stabilizer for hydrogen peroxide in hair bleaching preparations (Markland, 1966). In veterinary medicine, it is used as an analgesic an antipyretic agent (Stecher, 1968).

## 2.2 Occurrence

Phenacetin is not known to occur in nature.

## 2.3 Analysis

Methods of assay for phenacetin that meet regulatory requirements for pharmaceutical products include non-aqueous titration, gravimetric methods and UV spectrophotometry. A selective UV spectrophotometric method based on measurement of its oxidation products by cobaltic oxide can determine phenacetin in biological materials in the range of 5-50 µg/ml (Wallace et al., 1973).

A gas chromatographic method can determine phenacetin in mixtures with other drugs (Ryabtseva et al., 1970), and another determines phenacetin in urine and plasma (after its conversion to a silyl derivative) with a limit of detection of 0.05 µg/ml (Prescott, 1971).

Colorimetric methods include a determination of phenacetin in formulations with aspirin and codeine phosphate (Wosiak & Krzeminska, 1975), an assay for phenacetin based on its reaction with 1,2-naphthoquinone-4-sulphonate (Nomura et al., 1966) and a procedure based on oxidation of phenacetin with cerium (St. Ajer et al., 1969).

# 4. Comments on Data Reported and Evaluation

## 4.1 Animal data

In one limited study in which phenacetin was administered orally to rats, no carcinogenic effects were observed[1]. One putative metabolite of phenacetin, N-hydroxyphenacetin, is carcinogenic in rats after its oral administration: it produced hepatocellular carcinomas.

## 4.2 Human data

Available data indicate that heavy use of analgesic mixtures containing phenacetin is associated with papillary necrosis of the kidney and suggest a relationship between such use and the development of transitional-cell carcinoma of the renal pelvis.

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1 The Working Group was aware that several studies on the carcinogenicity of phenacetin are underway (IARC, 1976).

# Phenytoin and Phenytoin Sodium

## 1. Chemical and Physical Data

### Phenytoin

### 1.1 Synonyms and trade names

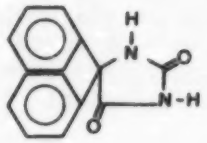
Chem. Abstr. Reg. Serial No.: 57-41-0

Chem. Abstr. Name: 5,5-Diphenyl-2,4-imidazolidinedione

Diphenylhydantoin; 5,5-diphenylhydantoin; 5,5-diphenylimidazolidin-2,4-dione; DPH; phanatine; phenantoine

Aleviatin; Antisacer; Denyl; Didan-TDC-250; Difhydan; Dihycon; Di-Hydan; Dihydantoin; Di-Lan; Dilantin; Dilantine; Dillantin; Dintoina; Diphantoin; Diphedan; Diphenin; Diphenine; Diphentoine; Diphentyn; Enkefal; Epanutin; Epilan; Epinat; Eptoin; Gerot-Epilan-D; Hidantal; Hydantin; Lepitoin; Sodanton; Tacosal; Zentropil

### 1.2 Chemical formula and molecular weight




$C_{15}H_{12}N_2O_2$ Mol. wt: 252.3

### 1.3 Chemical and physical properties of the pure substance

From Stecher (1968), unless otherwise specified

(a) Description: Powder

(b) Melting-point: 295-298°C

(c) Spectroscopy data: $\lambda_{max}$ 258 nm ($E^1_1$ = 28.1) in water (Weast, 1975); 264 and 257 nm ($E^1_1$ = 18.5 and 29.1) in methanol (Grasselli, 1973)

(d) Solubility: Practially insoluble in water; soluble in ethanol (1.7 g/100 ml) and in acetone (3.3 g/100 ml)

## 1.4 Technical products and impurities

Various national and international pharmacopoeias give specifications for the purity of phenytoin in pharmaceutical products. For example, phenytoin is available in the US as a USP grade containing 98.5-100.5% active ingredient on a dried basis with a maximum of 0.002% heavy metals, and as 50 mg tablets that contain 93-107% of the stated amount of phenytoin (US Pharmacopeial Convention, Inc., 1975). Oral suspensions of 6, 20 or 25 mg phenytoin per ml of a suitable medium are also available and contain 90-110% of the stated amount of phenytoin (National Formulary Board, 1970). Sustained release capsules of 50, 100, 125 or 250 mg phenytoin are also obtainable (Kastrup, 1975).

# Phenytoin sodium

## 1.1 Synonyms and trade names

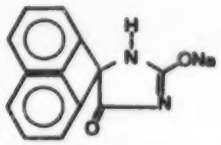
Chem. Abstr. Reg. Serial No.: 630-93-3

Chem. Abstr. Name: 5,5-Diphenyl-2,4-imidazolidinedione, monosodium salt

Diphenylhydantoin sodium; 5,5-diphenylhydantoin sodium; diphenylhydantoin sodium salt; 5,5-diphenylhydantoin sodium salt; phenytoinum sodium; sodium dipheylhydantoin; sodium 5,5-diphenylhydantoin; sodium 5,5'-diphenylhydantoin; sodium diphenylhydantoinate; sodium 5,5-diphenylhydantoinate; sodium 5,5-diphenyl-2,4-imidazolidinedione; odium phenytoin; soluble phenytoin

Alepsin; Antilepsin; Antisacer; Auranile; Citrullamon; Dantoin; Denyl; Difenin; Difetoin; Difhydan; Di-Hydan; Dihydantoin; Dilantin; Dilantin Sodium; Dintoina; Diphantoine; Diphedan; Diphenate; Diphenin; Diphentoin; Diphetine; Ditoin; Divulsan; Enkefal; Epamin; Epanutin; Epelin; Epifenyl; Epihydan; Epilan-D; Epilantin; Epinat; Eptoin; Fenantoin; Fenitoin; Fenytoine; Hidantal; Hydantin; Hydantoin; Hydantoinal; Idantoin; Idantoinal; Lepitoin; Minetoin; Novantoina; Novodiphenyl; Om-Hydantoine; Phenhydan; Saceril; SDPH; Sodanton; Solantoin; Solantyl; Sylantoic; Tacosal; Thilophenyt; Zentropil

## 1.2 Chemical formula and molecular weight



$C_{15}H_{11}N_2NaO_2$ Mol. wt: 274.2

## 1.3 Chemical and physical properties of the pure substance

From Stecher (1968)

(a) Description: White powder

(b) Solubility: Soluble in water at pH > 11.7 (1.7 g/100 ml) and in ethanol (10 g/100 ml); insoluble in ether and chloroform

(c) Stability: Gradually absorbs carbon dioxide on exposure to air, liberating phenytoin

## 1.4 Technical products and impurities

Various national and international pharmacopoeias give specifications for the purity of phenytoin sodium in pharmaceutical products. For example, phenytoin sodium is available in the US as a USP grade containing 98.5-100.5% active ingredient on a dried basis with a maximum of 0.002% heavy metals. Capsules are available in 30 or 100 mg doses and contain 93-107% of the stated amount of phenytoin sodium. Sterile phenytoin sodium suitable for parenteral use is available in 100 or 250 mg doses in solution containing 90-115% of the stated amount (US Pharmacopeial Convention, Inc., 1975). Phenytoin sodium is available in powder form in 1, 4 or 16 oz doses (Kastrup, 1975).

In the UK, preparations contain 98.5-101% active ingredient on a dried basis and 92.5-107.5% of the stated amount of active ingredient in tablets (British Pharmacopoeia Commission, 1973).

## 2. Production, Use, Occurrence and Analysis

For important background information on this section, see preamble, p. 15.

### 2.1 Production and Use

#### (a) Production

A method of preparing phenytoin was patented in the US in 1946 (Henze, 1946). In one commercially used method, benzaldehyde is converted to benzoin with sodium cyanide followed by oxidation with nitric acid to benzil; this is heated with urea in aqueous ethanolic potassium hydroxide and acidified to give phenytoin. In another method, phenytoin is obtained by heating urea with benzilic acid in acetic anhydride (Smith, 1966).

In a method of preparing phenytoin sodium, reported by Biltz in 1911, benzil was condensed with urea followed by treatment with sodium hydroxide (Stecher, 1968). This method is still used currently, in addition to a similar method which involves the following steps: benzaldehyde is converted to benzoin using sodium cyanide, followed by oxidation with nitric acid to give benzil; this is heated with urea in the presence of ethanolic sodium ethoxide or isopropoxide to give phenytoin sodium (Smith, 1966; Swinyard, 1975).

Commercial production of phenytoin was first reported in the US in 1946 (US Tariff Commission, 1948); only one US company reported production (see preamble, p. 15) in 1974 (US International Trade Commission, 1976a). US imports of phenytoin through the principal customs districts were 900 kg in 1972 (US Tariff Commission, 1973), 550 kg in 1973 (Us Tariff Commission, 1974) and 2,400 kg in 1974 (US International Trade Commission, 1976b).

Commercial production of phenytoin sodium was first reported in the US in 1938 (US Tariff Commission, 1939); only one US company reported production (see preamble, p. 15) in 1974 (US International Trade Commission, 1976a). US imports of phenytoin sodium were 1,500 kg in 1972 and in 1973 (US Tariff Commission, 1973, 1974) and 6,700 kg in 1974 (US International Trade Commission, 1976b).

No evidence was found that phenytoin is produced commercially in Japan. In 1975, 1,250 kg of this drug were imported; approximately 95% was converted into the sodium salt, and only 5% was used directly as an antiepileptic agent. Commercial production of phenytoin sodium was begun in 1951. In 1975, one company produced about 1,300 kg, of which about 1100 kg were used within the country.

Annual production of phenytoin and of phenytoin sodium in western Europe is estimated to be less than 1000 kg. Benelux, the Federal Republic of Germany and Italy are believed to be the major producing countries.

(b) Use

Phenytoin and phenytoin sodium are used largely in the treatment of grand mal and psychomotor seizures, often in combination with phenobarbital or other anticonvulsants. The oral dosage for adults and children over six years of age is initially 100 mg 3 times per day and can gradually be increased by 100 mg every two to four weeks until the desired response is obtained. Maintenance dosages usually range from 300 to 600 mg daily. Maintenance dosages for children under six are usually 3 to 10 mg/kg bw per day (American Society of Hospital Pharmacists, 1969).

Phenytoin sodium is also used for the control of status epilepticus. It is preferably administered intravenously, but can be administered intramuscularly if necessary. It can also be used for the prophylactic control of seizures in neurosurgery. It is administered intramuscularly during surgery and is continued during the post-operative period (Kastrup, 1975).

Phenytoin and phenytoin sodium have been proposed for use as cardiac depressants (anti-arrhythmic). The oral dose is usually 100 mg 2 to 4 times per day. An intravenous dose of 50 to 100 mg of the sodium salt is repeated every ten to fifteen minutes as necessary up to a total maximum dose of 10 to 15 mg/kg bw (US Pharmacopeial Convention, Inc., 1975).

Phenytoin has been used in the treatment of chorea or Parkinson's syndrome to control involuntary movements. Its use has been investigated for the treatment of trigeminal neuralgia, migraine, polyneuritis of pregnancy, acute alcoholism and certain psychoses (American Society of Hospital Pharmacists, 1969). Phenytoin sodium has also been suggested for use in the treatment of migraine, trigeminal neuralgia and certain psychoses. However, these uses are not yet approved by the US Food and Drug Administration (Swinyard, 1975).

Total US sales of phenytoin for use in human medicine are estimated to be less than 78,000 kg annually.

Phenytoin is used in veterinary medicine to control epileptiform convulsions in dogs (Swinyard, 1975). Phenytoin sodium has also been recommended as an anticonvulsant for dogs (Stecher, 1968).

## 2.2 Occurrence

Phenytoin and phenytoin sodium are not known to occur in nature.

## 2.3 Analysis

Methods of assay of phenytoin that meet regulatory requirements for pharmaceutical products are usually based on non-aqueous titrations; those for phenytoin sodium are usually based on gravimetric methods.

A collaborative study investigated a column chromatographic method to separate phenytoin sodium in capsules followed by direct ultraviolet quantitation (Cunningham et al., 1972).

A gas chromatographic method can determine phenytoin in serum in the range of 0.5-8.00 µg/ml (Brien & Inaba, 1974; Chin et al., 1972). Another gas chromatographic method has been developed to determine phenytoin as its alkyl derivatives after flash-heater alkylation with tetraalkyl ($C_1$-$C_7$) ammonium hydroxides (Giovanniello & Pecci, 1976; Pecci & Giovanniello, 1975). Comparisons have been made of gas chromatographic methods for the determination of phenytoin in serum with a spectrophotometric method (Janz & Schmidt, 1974) and with an enzymatic immunoassy method (Booker & Darcey, 1975). A spin immunoassay determination of phenytoin in serum has been reported to have a minimum sensitivity of 20-30 nmol (Montgomery et al., 1975).

Thin-layer chromatographic analyses of phenytoin can be made in pharmaceutical preparations (Prelini & Gerosa, 1975) and in blood and urine (Pippenger et al., 1969).

High-pressure liquid chromatographic methods use UV spectrophotometric detection to determine phenytoin and phenobarbital in plasma (Atwell et al., 1975), phenytoin and phenobarbital in plasma (Albert et al., 1973) and phenytoin in blood (Gauchel et al., 1973) and phenytoin, phenobarbital and primidone in blood (Kabra et al., 1976). The limit of detection of these methods is in the order of 1 µg/ml.

A mass fragmentographic determination of phenytoin and its metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin in human plasma has a limit of detection of 0.01 µg/ml (Hoppel et al., 1976).

An improved UV spectrophotometric method for the microdetermination of phenytoin in blood (Saitoh et al., 1973) and a simplified fluorimetric method for its determination in plasma (Dill et al., 1976) have been reported. A phosphorescence spectometry method for determination of phenytoin in blood has a detection limit of 0.05 µg/ml (Morrison & O'Donnell, 1974).

A complexometric determination of phenytoin has also been reported (Hentrich & Pfeifer, 1967).

The methods of analysis for phenytoin in biological samples would, in principle, also be applicable to phenytoin sodium.

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Phenytoin and its sodium salt are carcinogenic in mice following their intraperitoneal injection and oral administration, respectively: they produced lymphomas and leukaemias. Studies in which rats were given phenytoin by oral administration were of too short duration to allow an evaluation to be made.

### 4.2 Human data

An association has been observed in epileptic patients between the occurrence of lymphomas and long-term anticonvulsant therapy in which phenytoin alone or in combination with other anticonvulsants such as phenobarbital were given (see also monograph on phenobarbital and phenobarbital sodium, p. 157).

## 1. Chemical and Physical Data

Because polycyclic aromatic hydrocarbons are so well established experimentally as carcinogens, it is important to evaluate their capacity to induce cancer in man. There is a wealth of information concerning the effects of these chemicals on various tissues and organs of laboratory animals. In man, however, exposures have not been to individual chemicals but to combinations as they occur in soot, coal-tar, pitch and mineral oils, and also in environmental substances including tobacco smoke and exhaust. Environmental exposures to these substances are thus considered here separately from the monographs concerning the carcinogenicity of individual aromatic polycyclic hydrocarbons.

In this section human data, animal experiment data and chemical composition are examined in that order, since this is how our knowledge developed historically.

### 1. SOOT AND CARBON BLACK

### 1.1 Human data

Soot was first noted as a cause of skin cancer in man when Pott (1775) wrote that the disease "seems to derive its origin from a lodgment of soot in the rugae of the scrotum." Subsequently, cancer in chimney sweeps was described elsewhere on the skin and in internal organs (Butlin, 1892a).

It has been observed more recently (Sulman & Sulman, 1946) that soot formed by burning wood produced very little benzo(a)pyrene when compared with coal soot. The evidence for a relationship between exposure to soot and skin cancer was supported by the reduction of incidence of scrotal cancer in chimney sweeps after the institution of control measures in Great Britain (Schamberg, 1910). Skin cancer appeared in workers between eight and 47 years of age; whereas cancers following exposure to paraffin or tar occurred mainly in those between 34 and 60 years of age (Liebe, 1892). The 22-year difference in age at onset can be accounted for in part by the early age at which the chimney sweep began his apprenticeship: it was not uncomon for such service to begin at four years of age (Butlin, 1892b).

Commercially prepared soot, known as carbon black, produced no increase in cancer risk among workers (Ingalls, 1950; Tara,

1960); but cases have been described in the mixing of carbon black and oil in the rubber industry (Henry, 1946).

The apparent discrepancies in old and recent literature concerning the incidence of cancer following occupational contact with soot or carbon black are generally explained by new technology, advances in hygiene and enforcement of industrial legislation.

## 1.2 Animal data

The experimental production of skin cancer with extracts of soot was accomplished first by Passey (1922), who found that the most potent extracts were those which were free of acidic and phenolic compounds. He suggested that earlier unsuccessful attempts at tumour induction were due to lack of contact, penetration or duration of exposure to soot, to inappropriate samples of soot, or to inappropriate choice of the animal species tested.

The reported inability to induce cancer in mice by feeding carbon black (Nau et al., 1958a) or by applying it to the skin (Nau et al., 1958b) was overcome by administering solvent extracts by injection or by skin-painting (Falk & Steiner, 1952; Von Haam & Mallette, 1952). A benzene extract of oil shale soot (0.01% benzo(a)pyrene) mixed with Tween 60 produced lung cancer after intratracheal instillation in rats (Bogovski et al., 1970).

PAH have been identified in carbon black, processed rubber and rubber tyre extracts which were carcinogenic for mice (Falk et al., 1951).

## 1.3 Chemical composition

Benzo(a)pyrene is quantitatively the most important compound present in soot, although some other carcinogenic PAH have been detected in small amounts. It is not only a potent carcinogen, but also one for which the largest number of analytical methods is available.

Industrally, the synthesis of PAH is largely dependent upon specific procedures in which the combustion temperature of the organic matter determines the reaction products. In the range of 1100-1600°C organic compounds break down and, in the absence of sufficient oxygen, cracking occurs, with the release of hydrogen, carbon and CH radicals (Ellis, 1937). Polymerization of these free radicals takes place via "nascent acetylene", a term coined by Groll (1933).

Soot can contain benzo(a)pyrene, other carcinogenic compounds and compounds that are not carcinogenic. The carcinogens other than benzo(a)pyrene are of considerable interest with respect to their effect in man. They may contribute to the apparent contradictions in the literature concerning the variable cancer-producing activity of soot.

Falk & Steiner (1952) showed that carbon blacks of the furnace-black type contain several polycyclic aromatic hydrocarbons; the following seven were identified: pyrene, fluoranthene, benzo(a)-pyrene, benzo(e)pyrene, anthanthrene, benzo(g,h,i)perylene and coronene, and are readily extractable by a number of solvents from soot having an average particle diameter of 40 mμ or more (Kotin & Falk, 1959). The same compounds were extractable only in trace amounts from smaller sized particles; whereas none were obtained from channel blacks, which are prepared by a different process which yields particles of between 10 and 30 mμ average diameter. These substances do not release polycyclic hydrocarbons on solvent extraction but will absorb them from solution (Falk & Steiner, 1952).

Improvements in analytical techniques have increased the number of PAH detectable in carbon black. The newly identified compounds (including several benzofluoranthenes) do not appear to contribute significantly to the carcinogenic activity since they are either non-carcinogenic or, if carcinogenic, are present in small quantities. The inability to estimate the carcinogenic properties of "soot" or to evaluate the exposure risk associated with its industrial use can be appreciated when one contrasts a channel black from which no benzo(a)pyrene can be eluted with incinerator soot from which 2 mg benzo(a)pyrene/g of soot, i.e., 0.2%, were obtained (Sawicki, 1962).

## 2. Production, Use, Occurrence and Analysis

### 2.1 Human data

Butlin (1892c) described skin cancer among workers in the coal-tar and pitch industry. Largely through publications by Henry (1946, 1947) it was realized that the differing composition of tar products was related to the frequency of skin cancer among coal-tar workers. In 1907, the Workman's Compensation Act in England recognized officially that cutaneous epitheliomas could be caused by pitch or tarry substances. Ross (1948) classified

the products obtained on distillation of coal-tar as shown in Table II:

Table II

| Temperature | Compounds Produced |
|---|---|
| - 170°C | light oils; benzene, toluene, xylene |
| 170° - 230°C | middle oils; phenols, cresols, napthalene |
| 230° - 270°C | creosote oils, tar oils |
| 270° - 400°C | anthracene oils |
| | pitch residue |

Exposures to pitch occur not only among coal-tar workers, but also among optical lens grinders, electrical equipment workers and wharfmen, cable layers, net fixers and fabric proofers (Jenkins, 1948). Exposure to creosote oil occurs among brick and tile workers, as well as among timber-proofers (Henry, 1946).

In contrast with cancer occurring in chimney sweeps, occupational exposure to tar and pitch affects predominantly skin sites other than the scrotum. From 1920-45, pitch or tar was deemed responsible for 2229 of 3753 notified industrial skin cancers in Great Britain (Henry, 1946, 1947); while during the decade 1946-55, 2041 new cases of occupational skin cancer were notified in Great Britain, of which 1053 were atttributed to tar and pitch (Bogovski, 1960).

The majority of skin cancers in tar workers have been reported from England, but other reports have come from USA (Heller, 1930), Holland (de Vries, 1928), Germany (Volkman, 1875) and France (Manouvriez, 1876).

Human skin cancers have been described after exposures to creosote oil (O'Donovan, 1928; Cookson, 1924; Lenson, 1956) and to anthracene oil (Bridge & Henry, 1928; O'Donovan, 1921).

Kennaway & Kennaway (1947) described an increased frequency of lung cancer among workers exposed to coal gas and tar. Doll (1952) found that among 2071 male pensioners of a London gas company, the number of deaths from lung cancers was approximately double that expected from male inhabitants of London of the same age (25 deaths observed vs 13.8 expected). The investigation

concerned a multiplicity of occupations within the company, and it is probable that the risk was substantially greater for men most closely concerned with gas production.

In a further study, Doll et al. (1972) examined the mortality experience of groups of gas-workers in Great Britain over a period of 12 years. Among those categorized as coal carbonizing process workers, they found a significant excess of deaths from lung cancer (3.82 vs 2.13 per 100 000 per year); the rates for bladder cancer (0.40 vs 0.17) and cancer of skin and scrotum (0.12 vs 0.02) were also significantly higher than the national rates. Work as topman appeared to be particularly hazardous. The risk for lung cancer could not be related to any particular type of retort house. Among the by-products workers, there was no substantial evidence of any specific occupational hazard.

In Japan, 21 men exposed to coal-tar fumes in generator-gas plants developed lung cancer in a six-year period, a seeming excess over normal expectation (Kuroda & Kawahata, 1936). Kawai et al. (1967) observed that the longer the exposure the greater was the mortality from lung cancer, beginning ten years after exposure to coal-tar fumes.

In a British study of retort houses, certain areas were found to have 3 $\mu g/m^3$ benzo(a)pyrene, which was very much higher than the mean annual level for the city of London, away from the traffic, up to 1965. In the air above the retorts in the old horizontal retort houses where the processing temperature was 800 to 1000°C, the concentration of benzo(a)pyrene was over 200 $\mu g/m^3$. Such high levels were not found in vertical retort houses where the processing temperature was only 400 to 500°C (Lawther et al., 1965).

In a study of 58,528 employees of an American steelworks, Lloyd (1971) found that the mortality from respiratory cancer among coke plant workers was double that for steel workers as a whole. The excess was greater among those who had been employed directly at the ovens, particularly at the top of the ovens, among whom 15 lung cancer deaths occurred versus 1.5 expected.

Emissions from coke-ovens in the United States were analyzed for polycyclic aromatic hydrocarbons in 20 coke plants, and although their levels varied in each plant, similar ratios between benzo(a)pyrene, chrysene and benz(a)anthracene were found (Smith, 1970). In a report on a legal action involving one worker who developed lung cancer after working with tar, it was estimated that he could have inhaled 320 µg benzo(a)pyrene per hour. The tar contained 3% benzo(a)pyrene and gave off vapours at 300°C containing 4.4% benzo(a)pyrene (Bonnet, 1962).

## 2.2 Animal data

Crude coal-tar was first shown to be carcinogenic experimentally by Yamagiwa & Ichikawa (1915) who painted it on rabbits' ears for several months; and later Tsutsui (1918) and Murray (1921) produced similar results on the skin of mice. Coal-tar pitch and anthracene oil, fractions of coal-tar, were also shown to be carcinogenic (Kennaway, 1925); Bonser (1932) produced skin cancers by administration of blast furnace tar. Twort & Fulton (1930) demonstrated that the carcinogenic potency of tars prepared at temperatures of 500°C, 600°C and 750°C increased materially with the temperature of preparation.

Lijinsky et al. (1957) have found commercial creosote to be highly carcinogenic. They contained 2.75 g/l benz(a)anthracene, which is carcinogenic in the mouse (see monograph), and 1.27 g/l chrysene, a carcinogen for the mouse skin (see monograph). Benzo(a)pyrene and other pentacyclic PAH were present at much lower concentrations, i.e., about 50 mg/l.

## 2.3 Chemical composition

In an attempt to identify the responsible agent, carcinogenic coal-tar was fractionated and the aromatic fraction was found to be active. It possessed fluorescence, which led to the isolation and identification of benz(a)anthracene, a PAH with a characteristic fluorescence spectrum. On the basis of these findings, Kennaway & Hieger (1930), utilizing fluorescence spectroscopy, succeeded in isolating benzo(a)pyrene, which later proved to be carcinogenic, from coal-tar. With improved techniques, other PAH were isolated, among which dibenzo(a,h)pyrene, dibenzo(a,i)pyrene, benzo(b)-fluoranthene and dibenz(a,h)anthracene (Badger, 1962) were also shown to be carcinogenic constitutents.

Kennaway (1925) manufactured carcinogenic tars synthetically from a variety of sources such as isoprene, acetylene, skin, yeasts and cholesterol, and showed that carcinogenicity increased with the temperature involved in the distillation of tars.

Tar produced by pyrolysis of acetylene contained 2% benzo(a)-pyrene (Badger et al., 1960), and evidence has been presented for the pyrolytic formation of all known PAH encountered in soot (Badger, 1962). At 600-800°C, a yield of 0.1% to 0.15% of benzo(a)pyrene has been obtained through pyrolysis from isoprene (Gil-Av & Shabtai, 1963); the carcinogenic compound, dibenzo(a,i)-pyrene, can be made from 3-vinyl-cyclohexene at 700°C (Badger & Novotny, 1961). Oil shale tar produced at 400-500°C contains 0.001-0.02% benzo(a)pyrene (Bogovski, 1961).

## 3.1 Human data

Volkmann (1875) described scrotal cancers among workers producing paraffin by the distillation of coal-tar. Subsequently, Liebe (1892) noted the absence of such hazard among workers exposed to pure paraffin. Several investigators have since shown that cancers among paraffin workers are not due to the paraffin but to impurities in oils produced during processing (Leitch, 1922; Hendricks et al., 1959). Refined paraffin is free of PAH and does not induce skin cancer in mice (Shubik et al., (1962).

Bell (1876) first described cancer of the scrotum in a Scottish shale oil worker. In a 23-year period, 49 Scottish paraffin workers developed skin cancer of which 13 were scrotal (Henry, 1946).

The cotton mule spinning industry in Great Britain originally used shale oil for the lubrication of the spindles (Henry, 1946). The first case of death from scrotal cancer in a worker who used shale oil in mule spinning occurred in 1923 (Bridge & Henry, 1928). In the years 1920 to 1943, there were 1303 legally notified cases of skin cancer in the British mule spinning industry, including 824 of the scrotum. There were 575 fatal cases of scrotal cancer recorded between 1911 and 1938 (Henry, 1946).

In Great Britain, the Mule Spinning Regulations have ensured that since 1953 only oil drastically refined with sulphuric acid shall be used in mule spinning and that mule spinners shall be medically examined every six months. These measures, together with the marked decline of the process of mule spinning, have produced a sustained fall in the incidence of cancer of the scrotum in Great Britain.

Cutting oils used by workers to cut metals were found to increase the risk of skin cancer in Birmingham, England (Cruickshank & Squire, 1950); Cruickshank & Gourevitch, 1952), particularly among workers in automatic machine shops. Between 1950 and 1967, 187 cases of scrotal cancer occurred in this region, of which at least two-thirds could be attributed to oil (Waterhouse, 1971).

At the present time toolsetters and setter operators in automatic shops who use heat cutting oil have an increased risk of cancer. The work requires constant contact with the machines and consequent contamination with the oil. In the Birmingham area of England, a high frequency of skin and scrotal cancer from oil has occurred, particularly among bar automatic machine workers; but other engineering practices also present a cancer hazard, e.g., metal rolling, tube drawing, metal hardening and

machine operating. Although the major risk is from exposure to undiluted oils, emulsions have been incriminated occasionally. The industries most affected are those with automatic shops, such as nut and bolt manufacturers. Workers have also been affected after exposure during the changing of transformer oil in electrical sub-stations and during the painting or spraying of mould oil for brick- and tile-making or concrete moulding, in drop forging, rubber mixing, wire drawing, rope making and in the jute industry and from grease in metal working (Kipling, 1968).

In France, in the valley of the river Arve in the Savoy Alps, there have occurred since 1955 at least 60 cases of cancer of the scrotum together with many cases of cancer of the skin among the bar automatic machine workers (decolleteurs). The very high frequency in the relatively small population of the valley was observed mainly among the self-employed and workers in small premises (Thony & Thony, 1970). They were in contact with undiluted cutting oils.

Cancers of the larynx, lung and stomach have also been attributed to oil mist (Southam, 1928); and recently evidence has been produced that persons who developed cancer of the scrotum are significantly more liable to develop cancers at other sites, e.g., in the respiratory tract or upper digestive tract (Holmes et al., 1970).

## 3.2 Animal data

Leitch (1922) applied crude shale oil to mice and obtained tumour formation in the skin of 30 of the 74 mice that survived over 100 days. "Petroleum" oils were found to be less carcinogenic (Twort & Twort, 1931). Bingham & Horton (1966) showed that distillates of cutting oil are carcinogenic for the skin of mice even after sulphuric acid extraction; however, when they are extracted with furfural they become non-carcinogenic for mice over 80 weeks of skin application.

## 3.3 Chemical data

Mineral oils vary in their carcinogenicity and in their composition. Of particular interest are carcinogenic mineral oils that lack benzo(a)pyrene. Cook et al. (1958) isolated and identified components of various mineral oils, taking great care not to produce additional carcinogens during heating. In distilling below 250°C under reduced pressure, they produced a fraction free of benzo(a)pyrene which was carcinogenic for mice and rabbits in skin painting experiments. This observation was

confirmed by Bogovski (1959) in benzo(a)pyrene-free fractions of shale oil. The individual compounds which were separated included di- tri-, and tetramethylphenanthrenes, tetramethylfluorene, methylpyrene, benzo(a)fluorene and several heterocyclic compounds, such as dimethyldibenzothiophene, dimethylnapthothiophene and pentamethylcarbazole.

The carcinogenicity of mineral oil increases as the temperature is increased, as cracking occurs to form other compounds. Hueper & Cahnmann (1958) compared fractions with low and high boiling points, excluding those with benzo(a)pyrene, and found activity in six of them. One may conclude that mineral oils have various carcinogenic potencies depending on their origin, composition and treatment, and that some of the carcinogens may be three- or four-ring polycyclic aromatic hydrocarbons. Some of the fractions with carcinogenic activity may contain aliphatic hydrocarbons like dodecane, which possesses cocarcinogenic properties (Smith et al., 1951).

Other work (Badger, 1962) revealed that benzofluoranthenes, some of which are carcinogenic, are also present.

A report of the Medical Research Council (1968) stated that the carcinogenicity of crude oils appears to lie in impurities which boil above 350°C. From this fraction over 40 chemical compounds were isolated, several structurally similar to potent carcinogens. Compounds isolated included a wide range of aromatic hydrocarbons, e.g., di-, tri- and tetramethylnaphthalenes and phenanthrenes, chrysene and methyl derivative, perylene, triphenylene and tetramethylfluorene. Heterocyclic compounds included di- and teramethyldibenzothiophenes, thiobenzofluorene and tetra- and pentamethylcarbazoles.

The carcinogenicity of methyl derivatives of polycyclic and heterocyclic aromatic compounds will be considered in subsequent monographs.

## 4. Comments on Data Reported and Evaluation

PAH occur in many environmental situations (e.g., air, tobacco smoke or food) as a result of incomplete combustion, but their carcinogenic hazard to man cannot be estimated at present. The environmental exposure levels indicate that the hazard is relatively small compared with those found in certain occupations. However, this does not take into account the synergistic effects of other substances which might be present.

Satisfactory human epidemiological evidence is available concerning the synergistic effects of asbestos exposure and cigarette smoking, as well as for exposures to uranium ore dust and smoking.

Experimental confirmation of such synergistic effect is provided by the results of skin painting in mice, in which a 100-fold increase in skin cancer production has been observed when cigarette smoke condensate and equivalent benzo(a)pyrene concentrations were compared (Wynder & Hoffmann, 1967). As another example, a synergistic effect of dodecane and related substances on skin tumour induction in mice has been clearly demonstrated to be about 1000-fold for benzo(a)pyrene and about 100-fold for benz(a)anthracene (see monographs).

It is, therefore, obvious that no prediction as to human cancer risks can be made from a simple knowledge of the levels of PAH existing in the environment.

# Vinyl Chloride*

## 1. Chemical and Physical Data

### 1.1 Synonyms and trade names

Chem. Abstr. No.: 75-01-4

Chlorethane; chlorethylene; chloroethene; chloroethylene; ethylene monochloride; monochloroethene; monochloroethylene

VC; VCM; Vinyl chloride monomer; Vinyl C monomer

### 1.2 Chemical formula and molecular weight

$H_2C = CHCl$ $C_2H_3Cl$ Mol. wt: 62.5

### 1.3 Chemical and physical properties of the pure substance

(a) Description: A colourless, flammable gas under normal conditions of temperature and pressure but usually handled as a liquid under pressure

(b) Melting-point: -153.7°C

(c) Boiling-point: -13.9°C

(d) Density: $d_4^{20}$ 0.9121

(e) Refractive index: $n_D^{10}$ 1.4066

(f) Solubility: Slightly soluble in water (<0.11% w/w at 25°C (Hardie, 1964)); soluble in ethanol; very soluble in ether, carbon tetrachloride and benzene

(g) Volatility: Vapour pressure is 2660 mm Hg at 25°C.

(h) Chemical reactivity: Vinyl chloride monomer polymerizes in light or in the presence of a catalyst. On combustion, it is degraded mainly to hydrogen chloride, carbon monoxide, carbon dioxide and to traces of phosgene (O'Mara et al, 1971). It loses HCl on treatment with strong alkalis at high temperatures (Miller, 1969).

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* Considered by the Working Group in Lyon, 18-24 June, 1974. The Working Group was aware of many ongoing studies; however, this document is based upon published data or data already accepted for publication which were available at that time.

(i) Flash-point: -78°C

## 1.4 Technical Products and impurities

Vinyl chloride monomer is available commercially in cylinders or in bulk and is generally supplied as a liquid under pressure. The technical grade is 99.9% pure (Condensed Chemical Dictionary, 1971). Specifications for a typical commercial product call for maximums in mg/kg by weight of the following impurities: unsaturated hydrocarbons - 10; acetaldehyde - 2; dichloro compounds - 16; water - 15; hydrogen chloride - 2; nonvolatiles - 200; iron - 0.4. Phenol at levels of 25-50 mg/kg by weight is used as a stabilizer to prevent polymerization.

## 2. Production, Use, Occurrence and Analysis

Two review articles on vinyl chloride monomer have been published (Hardie, 1964; Keane et al., 1973).

### 2.1 Production and use[1]

The first synthesis of vinyl chloride monomer appears to have been made in 1835 by Regnault (Regnault, 1835). It has been produced commercially in the United States for at least 46 years (US Tariff Commission, 1928). Addition of hydrogen chloride to acetylene, formerly the most important route of synthesis, has been displaced by a method using the halogenation of ethylene; almost 90% of the vinyl chloride monomer produced in the US in 1971 was made from ethylene. In this process, ethylene is reacted with hydrogen chloride and oxygen to give ethylene dichloride, which is subsequently cracked to produce vinyl chloride monomer and hydrogen chloride.

In 1971, 10 US producers reported a total vinyl chloride monomer production of 1,969 million kg (US Tariff Commission, 1973). Preliminary data indicate that in 1972 US production amounted to 2,310 million kg (US Tariff Commission, 1974c) and in 1973 to 2,428 million kg (US Tariff Commission, 1974b). US imports of vinyl chloride monomer have been negligible; but in 1972, US exports were reported to have been 282 million kg, over half of which was exported to Norway, Belgium and Spain (US Department of Commerce, 1972).

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[1] Data from Chemical Information Services, Stanford Research Institute, USA

World production of vinyl chloride monomer in 1971 in various areas is estimated as follows (in millions of kg): Western Europe - 2,497; United States - 1,969; Japan - 1,275; Eastern Europe - 817; other areas - 499; total - 7,057. Countries producing vinyl chloride monomer (listed in decreasing order of estimated annual production in recent years) and the numbers of producers in each country are as follows: Japan (15), the Federal Republic of Germany (5), Italy (3), France (4), Belgium (3), the United Kingdom (4), The Netherlands (2), Brazil (3), Spain (3), Turkey (3), Taiwan (2), Argentina (2), Sweden (1), Mexico (1), USSR (2), South Korea (1), Finland (1), Czechoslovakia (1), Venezuela (1), Egypt (1), Thailand (1), Rumania (1), Chile (2), Greece (1) and Australia (1) (Keane et al., 1973).

In 1971, 77 million kg of vinyl chloride monomer were imported into the Common Market countries, as compared to an export volume of 52 million kg. Belgium/Luxembourg, Italy and The Netherlands were not exporters, whereas the Federal Republic of Germany and France were not importers; however, the situation is subject to rapid change due to the establishment of new plants and with changing short-term regional needs (European Communities, 1971). Japan exported 323 million kg of vinyl chloride monomer in 1972, principally to Taiwan (52%) and to the Republic of South Korea (30%).

At least 97% of the nearly 1,600 million kg of vinyl chloride monomer consumed in the US in 1971 was for the production of vinyl chloride homo-polymer and co-polymer resins. The remainder was used in a variety of applications, the most significant of which are in the production of methyl chloroform; as an additive to specialty coatings; and, in several products, as a component of certain propellant mixtures. Hardie (1964) has reported that vinyl chloride monomer has been used as a refrigerant, as an extraction solvent for heat-sensitive materials in the production of chloroacetaldehyde, an intermediate in the synthesis of sulpha drugs; however, no evidence was found that vinyl chloride monomer is presently being used for these purposes.

The polyvinyl chloride resins made from vinyl chloride monomer find their largest markets in the building and construction industries. Other important outlets are their use in household products, in consumer goods, in electrical applications, in packaging and in transportation (see Appendices A and B for additional information on the uses of polyvinyl chloride and vinyl chloride-vinyl acetate co-polymers).



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The consumption patterns for vinyl chloride monomer in Western Europe and Japan are believed to be similar to that in the US. An estimated 5% of the polymers made in Japan in 1972 were co-polymers of vinyl chloride monomer with other monomers.

In early April 1974, the US Environmental Protection Agency (EPA) announced that no new pesticide products containing vinyl chloride monomer as a propellant would be registered for use, and this body subsequently suspended from sale all pesticide aerosols containing vinyl chloride monomer for use in the home, in food-handling establishments, in hospitals or in other enclosed areas. Twenty-eight products were reported to be affected by the decision (US Environmental Protection Agency, 1974). In the USSR, vinyl chloride monomer has been banned for use in aerosol propellants, because of its hazardous effects (Grikitis, 1967).

In April 1974, three US manufacturers recalled from the market aerosol hairspray products containing vinyl chloride monomer, and the US Food and Drug Administration (FDA) was reported to have written to other manufacturers requesting that they identify products containing vinyl chloride monomer (Anon., 1974b).

In May 1974, the US Consumer Product Safety Commission issued an order proposing to ban the sale of all self-pressurized products containing vinyl chloride monomer which were intended for household use.

## 2.2 Occurrence

Vinyl chloride monomer is not known to occur in nature.

### (a) Occupational exposure

Cook et al. (1971) reported that the air concentration of vinyl chloride monomer in a polymerization reactor prior to ventilation is of the order of 7800 mg/m$^3$ (3000 ppm); that during the scraping procedure, 130-260 mg/m$^3$ (50-100 ppm); and that close to the hands during scraping, 1560-2600 mg/m$^3$ (600-1000 ppm). Lange et al. (1974a) found a concentration of 1560-2600 mg/m$^3$ (600-1000 ppm) vinyl chloride monomer in a polymerization reactor after washing. Concentrations of 50-800 mg/m$^3$ (20-312 ppm) vinyl chloride monomer have been found in the working atmosphere in a plant producing polyvinyl chloride (Filatova & Gronsberg, 1957); air concentrations of vinyl chloride monomer in working places in polyvinyl chloride-producing

factories were reported by these authors to range from 100-800 mg/m$^3$ (40-312 ppm) with peaks up to 87,300 mg/m$^3$ (34,000 ppm). Anghelescu et al. (1969) have reported values from 112-554 mg/m$^3$ (44-216 ppm). It has been estimated that 20,000 US workers, past and present, have been exposed to the chemical in manufacturing plants (Heath et al., 1974).

It has been reported that, on a time-weighted average, the concentration of vinyl chloride monomer to which coagulator operators are exposed ranges from 130-650 mg/m$^3$ (50-250 ppm). The close relationship between the concentrations of vinyl chloride monomer in air to which subjects have been exposed and that in their expired air after exposure has ceased suggests that monitoring of vinyl chloride monomer in air and breath analysis are both valid means of estimating the exposure of individuals to vinyl chloride monomer (Baretta et al., 1969).

Vinyl chloride monomer has been recognized as a potentially dangerous contaminant in manufacturing plants. In the USSR a maximum allowable concentration (MAC) of 30 mg/m$^3$ (12 ppm) has been recommended generally (Schottek, 1969), and in the Federal Republic of Germany a MAC of 260 mg/m$^3$ (100 ppm) has been introduced (Deutsche Forschungsgemeinschaft, 1973). In the US a maximum of 1300 mg/m$^3$ (500 ppm) in working atmospheres was allowed until April 1974 when the Occupational Safety and Health Administration (OSHA) of the US Department of Labor instituted a temporary emergency standard of 130 mg/m$^3$ (50 ppm) vinyl chloride monomer in the working atmosphere (US Code of Federal Regulations, 1974a). On May 6, 1974, the OSHA proposed a permanent standard which would set employee exposure at no detectable level, as determined by a sampling and analytical method capable of detecting concentrations of 1 ppm vinyl chloride monomer with an accuracy of 1 ppm ± 50%. This proposal also calls for monitoring, control methods, medical surveillance and records and reports (US Code of Federal Regulations, 1974b).*

Recently, it has been reported that polyvinyl chloride leaving certain manufacturing plants may contain 200-400 mg/kg (ppm) vinyl chloride monomer; on delivery to the customer this level is about 250 mg/kg (ppm); and after processing, levels of 0.5-20 mg/kg (ppm) are reached, depending on the method of fabrication (Anon., 1974e). Another source found 100 mg/kg (ppm) residual vinyl chloride monomer in polyvinyl chloride dispersions (Wilkinson et al., 1964).

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* See also p. 310

(b) Air and rain

In early May 1974, an official of the EPA estimated that US plants were discharging 90 million kg vinyl chloride monomer into the atmosphere annually (Anon., 1974c). The EPA is also reported to have found 6% losses of vinyl chloride monomer from polyvinyl chloride-producing plants and concentrations of 2.6-5.2 mg/m$^3$ (1-2 ppm) in the air near these plants (Anon., 1974d). On May 30, 1974, that body requested US companies making vinyl chloride monomer and polyvinyl chloride to provide process, emission and air quality data on their plants for possible use in establishing air pollution control standards (Anon., 1974f).

It has been reported (US Federal Register, 1974) that the use of aerosol products in enclosed spaces, even in short bursts (e.g., 30 seconds), could result in air concentrations of vinyl chloride monomer as high as 1000 mg/m$^3$ (400 ppm) and that these levels could persist for several hours after spraying.

(c) Food

In May 1973, a branch of the US Treasury Department banned the use of polyvinyl chloride for the packaging of alcoholic beverages (Anon., 1973b). This action was a result of studies reported by the FDA indicating that levels of up to 20 mg/kg (ppm) vinyl chloride monomer were present in alcoholic beverages packaged in this material (Anon., 1973a).

## 2.3 Analysis*

Unsaturated polymerizable compounds such as vinyl chloride monomer can be separated and identified as mercuric acetate adducts by thin-layer chromatography on silica gel (Braun & Vorendohre, 1964). Methods have also been described for the separation and determination of mixtures of halogenated compounds containing vinyl chloride monomer (Hollis, 1966; Hollis & Hayes, 1962), and one is available for the determination of residual vinyl chloride monomer in polyvinyl chloride dispersions (Wilkinson et al., 1964).

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* See also p. 310

Infra-red spectroscopy using a long-path cell has been used for time-weighted monitoring in factory atmospheres (Baretta et al., 1969). Although the limit of detection was given in this report as 5 ppm, another source (Stewart et al., 1965) gave limits of detection of 0.26-26 mg/m$^3$ (0.1 and 10 ppm) vinyl chloride monomer in breath but stated that a sample 5-10 times 10 ppm is necessary for positive confirmation of vinyl chloride monomer. The analysis made by Stewart et al. (1965) involved chromatography and infra-red spectroscopy.

Vinyl chloride monomer can be detected at levels as low as 130 mg/m$^3$ (50 ppm) by a Tilley Refrigerant Leak Detector Lamp (Christie et al., 1965); it can also be determined by gas chromatography (Galipern et al., 1968; Hinshaw, 1966; Popova et al., 1967) and by gas-liquid chromatography (Hollis & Hayes, 1962). Porous polyaromatic polymer bead columns have been employed to concentrate gas samples at room temperature prior to their gas-chromatographic determination (Hollis, 1966; Williams & Umstead, 1968). The presence of vinyl chloride monomer in air samples has also been determined by colorimetry (Gronsberg, 1966).

## 4. Comments on Data Reported and Evaluation

### 4.1 Animal data

Vinyl chloride monomer (VCM) is carcinogenic im mice and rats following exposure by inhalation. The tumours in mice were mainly lung tumours, mammary carcinomas and angiosarcomas (malignant haimangioendotheliomas) of the liver. Angiosarcomas of the liver and other organs, Zymbal gland carcinomas and nephroblastomas occurred in exposed rats. Preliminary studies have suggested that VCM also produces subcutaneous angiosarcomas in the offspring of rats that have been exposed during pregnancy.

### 4.2 Human data

In view of the extreme rarity of angiosarcoma of the liver in the general population, the observation of 16 cases in workers exposed to vinyl chloride monomer during the polymerization process is evidence of a causal relationship.

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* This evaluation is based upon published data or data accepted for publication up to 26 June 1974.

# Part II

## Agency Submissions, as Received, on the 26 Chemicals of Industrial Processes Considered in This Report

CONSUMER PRODUCT SAFETY COMMISSION

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Aurodix trisulfo | 1327-33-1 | Almost totally imported from Europe | | Possible use in glass and ceramics | | Possible extent of consumer exposure to be determined | | | | | | | | Economic research studies being conducted by CPSC | |
| Auramine | | Not known | | Dye, dye intermediate--intended for industrial use only, e.g. for textiles, paper, leather | | Exposure to auramine in consumer products only through residual dyes on textiles, paper, leather, etc. | Dermal | | | | | | | Any action deferred until completion of Interagency Testing Committee dye evaluation project | |
| Cadmium (elemental) | 7440-43-9 | --4-5 million lbs/yr. used in commercial electroplating-solder use exclusively for jewelry and silversmithing<br>--degree of consumer use unknown<br>--1 million lbs/yr. used in plastic stabilizers | | Used in electroplating wide variety of consumer products--some use in silver solder--use in pigments, plastic stabilizers, batteries | | 100-200 million persons exposed to electroplated products--exposure to cadmium from such products unknown | | | | | | | | CPSC Staff investigation of solder use in progress | |
| | | | | | | | | | | | | | | | |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Asbestos | 1332-21-4 | Units of individual products containing asbestos to be determined by CPSC research in FY 80 | | In large number of consumer products (appendices A & B) | | Essentially entire populations exposed to consumer products containing asbestos in some form. If asbestos not in or not capable of being converted to respirable form, then actual exposure lower | Inhalation | | | | | CPSC | FHSA | Ban in effect as of 1972 on general use garments containing asbestos (other than garments for use as personal protection against thermal injury and so constructed that the asbestos fibers will not become airborne under reasonably foreseeable conditions of use) | Essentially eliminated potential for exposure to asbestos in general use garments |
| | | | | | | | | | | | | | CPSA | Ban in effect as of 1978 on patching compound and gas log embedding materials containing asbestos. | Prior to ban 7.5 million units of asbestos containing patching compounds were produced annually with 5-10 million persons exposed. Prior to ban 0.5-1.5 million persons exposed to embedding materials. Since ban, no additional persons exposed |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Asbestos (Continued) | | | | | | | | | | | | | | Voluntary recall or repair of asbestos containing hair dryers initiated in 1979 by 37 firms; voluntary discontinuance of use of asbestos by major hair dryer firms in 1979, both as a result of CPSC action.<br><br>Advance notice of Proposed Rulemaking (10-79) seeking information on use of asbestos in consumer products; describing purpose of approach of seeking elimination of all non-essential uses of asbestos in consumer products from which asbestos fibers are released during use; stating intent to issue general and specific orders. | As of September, 1979, 1.5 million units returned for repair, replacement or refund. |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Benzene | 71-43-2 | 11 million gallons of products containing 0.1% or more benzene as contaminant (20 million units) is estimated to be produced annually | | No longer used as intentional ingredient in consumer products containing petroleum distillates | | 20 million persons annually exposed to consumer products containing benzene as contaminant, assuming 1 unit per person per year | Inhalation dermal | | | | | CPSC | Consumer Product Safety Act (CPSA) | Proposed ban of benzene as intentional ingredient in consumer products and ban of products containing 0.1% or more by volume of benzene as contaminant | Because benzene no longer used as intentional ingredient, perhaps as a result of the publication of the proposed regulation 400,000-800,000 persons no longer exposed |
| | | | | | | | | | | | | | Federal Hazardous Substances Act (FHSA) | Products containing 5% or more benzene by weight must bear precautionary labelling--products containing 10% or more benzene by weight must bear additional precautionary labelling | Difficult to assess effectiveness of labelling regulations |
| | | | | | | | | | | | | | Poison Prevention Packaging Act (PPPA) | Safety packaging required for prepackaged liquid solvents, paints, other similar surface coating materials that contain 10% or more by weight benzene, toluene, xylenes, petroleum distillate mixtures thereof and have viscosity of less than 100 Saybolt Universal Seconds at 100°F | Estimated that packaging effectiveness for all products covered by safety packaging regulations was 35% over a three year period 1973-76 Cannot make estimate as to effectiveness of regulation in reducing poisonings from benzene containing products per se |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Benzidine | 92-87-5 | | | Not used commercially in consumer products--may exist as a contaminant in benzidine based dyes | | Consumer exposure to residual levels in textiles or benzidine-based dyes | | | | | | | | | |
| Benzidine-based dyes | | 1.4 million lbs. in 1977 (only one domestic manufacturer | 76,300 lbs. (1977) | In textiles, fabric dyes for use by consumers-arts and crafts dyes market | | Degree of consumer exposure to dyes not yet determined none of three companies marketing fabric dyes through retail outlets presently use benzidine-based dyes about 20,000 lbs of total dyes sold per year through arts and crafts market | | | | | | CPSC | Consumer Product Safety Act (CPSA) | Petition from Center for Occupational Hazards and three other groups to ban consumer use of benzidine-based as well as dyes based on o-tolidine and dianisidine under CPSA being addressed by CPSC staff, Various regulatory options being developed | |
| Benzidine-based pigments | | No domestic production or imports since 1974 | | | | | | | | | | | | | |
| Cadmium sulfate | 10124-36-4 | 1-2 million tons used as stabilizer in plastics for all uses, not just consumer products | | May occur in plastics, especially polyvinyl chloride as stabilizer --declining use in plastics. Not used in water pipes because of leaching problem--may appear in pigments | | Extent of consumer exposure to be determined | | | | | | | | CPSC staff investigation in progress | |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Cadmium sulfide | 1306-23-6 | 1.26 million lbs/yr. for all uses | | Pigment in inks and artists color; possible use in glass, ceramics, textiles, paper, and phosphorescent materials | | Consumer exposure to be determined | | | | | | | | CPSC economic study ongoing | |
| Calcium chromate | 13765-19-0 | Amount used in consumer products to be determined | | Possible use in paint pigments (largely as corrosion inhibitor) --use in protective coatings | | Consumer exposure to be determined | | | | | | | | CPSC economic study ongoing | |
| Chromic oxide | 1308-38-9 | Production for consumer products to be determined | | May be used in paint, pigments, Portland cement, refractory brick, leather goods | | Exposure of consumers to products to be determined | | | | | | | | Ongoing economic study | |
| Chromium (elemental) | 7440-47-3 | Amount used in electroplating not determined | | Widely used in electroplating products | | 200 million persons exposed to such products | | | | | | | | | |
| Chromium dioxide | 12018-01-8 | | | Magnetic tapes | | Exposure of consumers to products to be determined | | | | | | | | Economic study in process | |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Sodium dichromate | 10588-01-9 | | | Leather tanning, roofing materials, chromic pigment, used in paints, printing inks for coloring paper, rubber, linoleum, floor tile | | Exposure of consumers to products to be determined | | | | | | | | Economic study in progress | |
| 2-Naphthylamine | | No longer produced in the US | | Industrial dyes | | Consumer exposure may take place through loss of dyes from dyed consumer products | | | | | | | | Deferred pending recommendations from Interagency Testing Committee dye evaluation project | |
| Vinyl chloride | 75-01-4 | | | Formerly used as propellant for aerosol consumer products--only occurrence in consumer products may be as low level contaminant in vinyl chloride copolymer and homopolymer resins | | Exposure to VCM as contaminant in consumer products believed to be insignificant | | | | | | CPSC | FHSA | Ban on use of vinyl chloride as aerosol propellant in household products | Prior to actions by CPSC, FDA, EPA to ban vinyl chloride as an aerosol propellant, 3-4 million total units of aerosols containing vinyl chloride propellant were sold annually--as a result of the bans, 1-6 million persons are no longer exposed to vinyl chloride as a propellant |
| | | | | | | | | | | | | | | | |

# CONSUMER PRODUCT SAFETY COMMISSION ADDENDUM

| Chemical | Use of Chemical in Consumer Products | Estimated Production of Chemical for Consumer Product Uses | Estimated Current Exposure | Remarks |
|---|---|---|---|---|
| Arsenic Trioxide | Possible use in glass and ceramics | To be determined. Almost wholly imported from Europe | To be determined | Economic research studies being conducted by CPSC |
| Auramine | Dye, dye intermediate - in the course of research performed under contract to CPSC, all producers contacted stated that the dyes were intended for industrial use only - for textiles, paper, leather, etc. | Not known | Only through residual dyes on textiles, paper, leather, etc. | Any action deferred until completion of Interagency Testing Committee dye evaluation project. |
| Cadmium (elemental) | Electroplating in wide variety of products<br><br>Some use in silver solder, pigments, plastic stabilizers, batteries | 4-5 million lbs/yr used in commercial electroplating<br><br>Used in solder exclusively for jewelry and silversmithing - degree of consumer use unknown<br><br>1 million kg/yr used in plastic stabilizers. | 100 million to 200 million persons exposed to electroplated products. Amount of exposure to cadmium through these products unknown. | CPSC staff investigation of solder use in progress |
| Cadmium Sulfate | May occur in plastics, especially polyvinyl chloride, as a stabilizer-declining use in plastics. Not used in water pipes since it leaches out of pipes. May appear in pigments. | 1-2 million tons used as stabilizer in plastics for all uses, not just in consumer products | To be determined | CPSC staff investigation in progress |
| Cadmium Sulfide | inks and artists colors as pigment. Possible other uses are in glass, ceramics, textiles, paper and phosphorescent materials. | 1.26 million lbs/yr for all uses | To be determined | Economic study ongoing |
| Calcium Chromate | Possible use in paint pigments (largely used as a corrosion inhibitor) protective coatings | To be determined | To be determined | Economic study in process |

| Chemical | Use of Chemical in Consumer Products | Estimated Production of Chemical for Consumer Product Uses | Estimated Current Exposure | Remarks |
|---|---|---|---|---|
| Chromic Oxide | May be used in paint pigments, Portland cement, refractory brick, leather goods | To be determined | To be determined | Ongoing economic study |
| Chromium (elemental) | Widely used in electroplating products | Amount used in electroplating not determined | 200 million persons | --- |
| Chromium Dioxide | Magnetic tapes | To be determined | To be determined | Economic study in process |
| Sodium Dichromate | Leather tanning, roofing materials, chrome pigment used in paints, printing inks for coloring paper, rubber, linoleum, and floor tile | To be determined | To be determined | Economic study underway |
| 2 -Naphthylamine | Industrial dyes | No longer produced in U. S. | Consumer exposure may take place through loss of dyes from dyed consumer products | Deferred until recommendations made by Interagency Testing Committee dye evaluation project |
| | | | | |

ENVIRONMENTAL PROTECTION AGENCY

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Aflatoxins<br>B-1<br>1162-65-8<br>B-2<br>7220-81-7<br>G-1<br>1165-39-5<br>G-2<br>7241-98-7 | Not manufactured-<br>contaminant in nature of many foodstuffs | Because aflatoxins are naturally occurring food contaminants, EPA has minimal regulatory interest in them. The Agency has no indication of their presence in effluents, emissions, or wastes from food processing plants. | | |
| 4-Aminobiphenyl<br>92-67-1 | No production reported to TSCA Inventory | IARC and OSHA indicate a workplace hazard associated with production of diphenylamine. EPA has no data to document a controllable environmental hazard at these production facilities or involving this chemical. | | |
| Arsenic<br>7440-38-2 | Production aggregated for:<br>Arsenic<br>Arsenic pentoxide<br>Arsenic trioxide<br>Potasium arsenate<br>Sodium arsenate<br>Sodium arsenite<br><br>Domestic production:<br>69,717,000 lb*<br>Imports:<br>19,877,500 lb*<br>*some site limitations | Interim primary drinking water water regulation<br><br>Effluent guidelines for certain industrial categories | Establishes maximum contaminant level of 0.05 mg/l. Does not address carcinogenicity. This regulation is under review, and may be revised at a later date.<br><br>Establishes control over arsenic in certain effluent through permits issued under the NPDES. Carcinogenicity is not a factor in developing effluent guidelines. | 40 CFR #141.11<br><br>40 CFR 415, 421, 429, 430 (portions) |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Arsenic (Continued) | 41 producers and importers in 10 SFR's<br><br>Public record only | <br><br>Assessments in progress to determine if Clean Air Act or TSCA controls may be warranted. | | |
| Arsenic pentoxide 1303-28-2 | Aggregated under arsenic | Hazardous spill regulation designating harmful quantities, requiring reporting of spills, and imposing penalties.<br><br>RPAR issued regarding eleven inorganic arsenical pesticides | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity.<br><br>Rebuttal data are under review. The notice of proposed determination is scheduled for publication in 6/80. | 40 CFR 117<br><br>42 FR 202, p. 48267 et seq. |
| Arsenic trioxide 1327-53-3 | Aggregated under Arsenic<br><br>OPP notes that arsenic trioxide is the source material for 97 percent of arsenic products. | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties.<br><br>Ban on use of formulations containing more than 1.5 percent arsenic trioxide in households and grazing areas. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity.<br><br>Some reduction in use. | 40 CFR 117<br><br>Written notice to registrants 8/68. Not published in FR by USDA. Current procedures would require such publication. |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Arsenic trioxide (Continued) | | Registrations of products for three uses voluntarily cancelled by producers. | Minimal reduction in exposure potential as these uses accounted for only a small portion of production. | 42 FR 177, p. 45944 |
| | | RPAR issued regarding 11 inorganic arsenical pesticides | Rebuttal data are under review. The notice of proposed determination is scheduled for publication in 6/80. | 42 FR 202, p. 48267 et se |
| Exposure:<br>Type of population / Route / Levels<br>Young adult males — diet — 0.10-0.16 ppm<br>Toddlers — diet — 0.100-0.180 ppm<br>Infants — diet — trace<br>Based on 2-week prepared samples; not translated to mg/kg body weight or comparable dose level.<br>Data from FDA, published by EPA. | | | | |
| Potassium arsenate 7784-41-0 | Aggregated under Arsenic | Hazardous spill regulation designating harmful quantity, requiring reporting of spills, and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals, does not address carcinogenicity. | 40 CFR 117 |
| Sodium arsenate 7631-89-2 | Aggregated under Arsenic | Hazardous spill regulation designating hazardous quantity, requiring reporting of spills, and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Sodium arsenate (Continued) | | RPAR issued regarding 11 inorganic arsenical pesticides. | Rebuttal data are under review. The notice of proposed determination is scheduled for publication in 6/80. | 43 FR 202, p. 48267, et seq |
| Sodium arsenite 7784-46-5 | Aggregated under Arsenic | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| | | Ban on use of formulations containing more than 2.0 percent sodium arsenite in households or grazing areas. | Some reduction in use. | (Written notice to registrants 8/68. Not published in FR by USDA. Current procedures would require such publication.) |
| | | Registrations of products for two uses voluntarily cancelled by producers. | Some reduction in use | 42 FR 48, p. 13579 |
| | | RPAR issued regarding 11 inorganic arsenical pesticides | Rebuttal data are under review. The notice of proposed determination is scheduled for publication in 6/80. | 43 FR 202, p. 48267, et seq |
| | | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Asbestos<br>1332-21-4 | Domestic consumption (1976)<br>1,452,000 lb (Bureau of Mines) | National Emissions Standards for Hazardous Air Pollutants, addressing several industrial categories | Some reduction in emissions, largely through engineering and practice controls. The carcinogenic risk of airborne asbestos was a major factor in the promulgation of those regulations. The absence of economically feasible analytical methods precluded setting of numerical standards. | 40 CFR 61. 20-25 |
| Types:<br>Crocidolite<br>12001-28-4<br>Chrysotile<br>12001-29-5<br>Amosite<br>1272-73-5<br>Actinolite<br>13768-00-8<br>Tremolite<br>14567-73-8<br>Anthophyllite<br>17068-78-9 | Some importers reported for the TSCA Inventory (but not volumes)<br><br>Public Record Only<br><br>142 plant sites in seven SFR's are subject to NESHAPs for asbestos | | | |
| | | Effluent guidelines for the asbestos industry and for asbestos mining/ milling. | Do not directly address asbestos, control of suspended solids as a condition of NPDES permits may afford a degree of control. | 40 CFR 427, 436 (portions) |
| | | Water Quality Criteria | Proposed 10/79. Subject to revision in final. | 44 FR 91, p. 56628, et seq |
| | | Voluntary program of abatement of asbestos in schools. | High interest in acting to encapsulate or replace asbestos-containing materials in school buildings. | 44 FR p. 17791 |
| | | Advance notice of proposed rulemaking | Seeks information on asbestos uses that would be good candidates for regulation. Issued in conjunction with CPSC. | 44 FR 202, p. 60056, et seq. |

| Substance (CAS #) | Production (including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Auramine<br>492-80-8 | No domestic production reported<br><br>Imports: 500 lb*<br>*some site limitations<br><br>Two importers in one SFR<br><br>Public Record Only | The Interagency Testing Committee is considering a number of chemicals used in dyemaking for Test Rule recommendations because of the general inadequacy of risk data regarding this use category of chemicals. Some test rule recommendations have already been made, and more may follow. | | |
| Benzene<br>71-43-2 | Domestic production 16,207,711,500 lbs*<br><br>Imports 2,815,501,500 lbs*<br><br>*some site limitations<br><br>97 producers and importers in 10 SFRS.<br><br>Public Record Only | Hazardous spill regulation designating harmful quantity, requiring reporting of spills, and imposing penalties<br><br>Water Quality Criteria<br><br>Listed for phased National Emission Standards for Hazardous Air Pollutants | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity.<br><br>Proposed 3/79. Subject to revision in final<br><br>First of several proposed standards in final review. Others will follow during next two years on present plan. These will be proposed as engineering controls in several industries from which benzene is emitted into the air. | 40 CFR 117<br><br>44 FR 52, p. 15296 et seq<br><br>42 FR 110, p. 29332-3 |
| | | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Benzidine<br>92-87-5 | Domestic production 500 lbs<br><br>Imports: None reported.<br><br>One producer in 1 SFR.<br><br>Public Record Only | Toxic Pollutant Effluent Standard<br><br>Water Quality Criteria<br><br>Mass balance study of benzidine and derivative to identify subjects for possible regulatory attention. | Manufacture has dropped considerably since 1977 promulgation.<br>Proposed 10/79. Subject to revision in final | 40 CFR 129. 104<br><br>44 FR 191. p. 56628 et seq. |
| Bis(chloromethyl ether)<br>542-88-1 | Domestic production: 550,000 lbs<br><br>Imports: None reported<br><br>One producer in one SFR<br><br>Public Record Only | Water Quality Criteria for chloroalkyl ethers<br><br>Assessments are in progress to determine if NESHAPs or other Clear Air Act regulations would be appropriate for BCME. | Proposed 10/79. Subject to revision in final. Specifically addresses BCME | 44 FR 191, p. 56628 et seq. |
| | | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Cadmium<br>7440-43-9 | Production aggregated for:<br>Cadmium<br>Cadmium acetate<br>Cadmium carbonate<br>Cadmium chloride<br>Cadmium flouborate<br>Cadmium nitrate<br>Cadmium oxide<br>Cadmium sulfate<br>Cadmium sulfide | Interim Primary Drinking Water Regulation | Establishes maximum contaminant level of 0.010 mg/l. Does not address carcinogenicity. This regulation is under review, and may be revised at a later date. | 40 CFR 141.11 |
| | | Effluent guidelines for certain industrial categories | Establishes control over cadmium in certain effluents through permits issued under NPDES, Carcinogenicity is not a factor in developing effluent guidelines | 40 CFR 413, 421, 440 (portions) |
| | Domestic production: 25,199,000 lbs* | | | |
| | Imports: 3,153,000 lbs* | Water Quality Criteria | Proposed 3/79. Subject to revision in final. | 44 FR 52, p. 15926 et seq. |
| | * some site limitations | | | |
| | 63 producers and importers in 10 SFR's | RPAR issued against cadmium containing pesticides. | Rebuttal data are under review. Further action deferred because of lack of resources. | 42 FR 206, p. 56574 et seq. |
| | Public Record Only | Under assessment to determine if Clean Air Act of TSCA regulations would be appropriate for cadmium. | | |
| Exposure: | | | | |
| Type of population / Route / Levels | | | | |
| Young adult males / diet / 0.05-0.14 ppm | | | | |
| Toddlers / diet / 0.05-0.08 ppm | | | | |
| Infants / diet / 0.05-0.10 ppm | | | | |
| Based on 2-week prepared samples; not translated to mg/kg body weight or comparable dose level. Data from FDA, published by EPA | | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Cadmium acetate 543-90-8 | Aggregated under cadmium | Hazardous spill regulation designating harmful quantity, requiring reporting of spills, and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| Chloramphenicol | Not reported for the TSCA Inventory | Because chloramphenicol is a pharmaceutical with no other known use, EPA has minimal regulatory interest in it. The Agency has no indication of its presence in effluents, emissions or wastes from pharmaceutical manufacturers. | | |
| Chloromethyl methyl ether 107-30-2 | Domestic production: quantity not reported.<br><br>Imports: None reported.<br><br>4 Producers in 4 SFR's.<br><br>Public Record Only | Assessments are in progress to determine if NESHAPs or other Clean Air Act regulations would be appropriate for CMME.<br><br>To date, EPA has been primarily concerned about BCME, which is frequently cited as a contaminant of CMME. Actions, such as development of water quality criteria, taken regarding chloralkyl ethers will undoubtedly have implications for CMME, even if this compound is no specifically named. | | |
| | | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Chromium<br>7440-47-3 | Production aggregated for:<br>Chromium<br>Barium chromate<br>Chromic oxide<br>Chromium acetate<br>Chromium trioxide<br>Lead chromate<br>Potasium chromate<br>Potasium dichromate<br>Sodium chromate<br>Sodium dichromate<br>Strontium chromate | Interim Primary Drinking Water Regulation | Establishes maximum contaminant level of 0.05 mg/l. Carcinogenicity of hexavalent chromium was considered. | 40 CFR 141.11 |
| | | Effluent guidelines for certain industrial categories. | Establishes control over chromium in certain effluents through permits issued under the NPDES. Carcinogenicity is not a factor in developing effluent guidelines, although the generally higher risks associated with hexavalent chromium were addressed | 40 CFR 409, 413, 415, 419, 420, 423, 424, 425 (as chrome) 428, 429, (portions) |
| | Domestic production: 914,457,000 lbs | | | |
| | Imports: 113,816,500 lbs | Water Quality Criteria | Proposed 10/79. Addresses carcinogenicity of hexavalent chromium. Subject to revision in final. | 44 FR 191, p. 56628, et seq. |
| | 95 producers and importers in 7 SFRs. | | | |
| | Public Record Only | Assessments to determine if TSCA controls would be appropriate results in a finding that the primary problem area was the workplace. Results were given to OSHA in May 1978. No further action contemplated. | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Potassium chromate 7789-00-6 | Aggregated under chromium | Hazardous spill regulations designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| Potassium dichromate 7778-50-9 | Aggregated under chromium | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| | | Effluent guidelines for manufacture of potassium dichromate | Controls chromium in effluent through permits issued under the NPDES. Carcinogenicity is not a factor in developing effluent guidelines. | 40 CFR 415. 120-126 |
| Sodium chromate 10588-01-9 | Aggregated under chromium | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Sodium dichromate 10588-01-9 | Aggregated under chromium | Hazardous spill regulation designating harmful quantity, requiring reporting of spills, and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| | | Effluent guidelines for manufacture of sodium dichromate | Controls chromium in effluents through permits issued under the NPDES. Carcinogenicity is not a factor in developing effluent guidelines. | 40 CFR 415, 170-176 |
| Strontium chromate 7789-06-2 | Aggregated under chromium | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| Cyclophosphamide 50-18-0 | Not reported for TSCA Inventory | As a pharmaceutical, cyclophosphamide is of secondary regulatory interest to EPA. The Agency has no data to indicate its presence in effluents or emissions from pharmaceutical manufacturers. This chemical was proposed for listing as a hazardous waste in December 1978 | | 43 FR 243, p. 58954, et seq. |
| Diethylstibestrol 56-53-1 | Not reported on TSCA Inventory | As a food additive and pharmaceutical, DES is of secondary regulation interest to EPA. The Agency has no data to indicate its presence in effluents or emissions from appropriate manufacturers. This chemical was proposed for listing as a hazardous waste in December 1978. | | 43 FR 243, p. 58594, et seq. |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Hematite<br>1309-37 1 | Domestic production: 1,135,632,000 lbs<br><br>Imports: 711,022,500 lb*<br><br>*some site limitations<br><br>71 producers and importers in 10 SFRs.<br><br>Public Record Only | Hematite is viewed by EPA as primarily within the jurisdiction of MHSA (mining and milling) or OSHA (iron production). Some effluent guidelines address the ferric ore mining milling, and refining categories, but do not address hematite, per se. Control of total suspended solids through NPDES permits may afford some control of hematite pollution. In view of the indication that the primary cancer risk is to workers, it is unlikely that EPA will assume further jurisdiction over hematite. | | |
| Isopropyl oils no CAS # | Isopropyl oils are indicated as being by-products of the manufacture of isopropyl alcohol by the strong acid process. Data for isopropyl alcohol follow, but there is no indication as to what, if any, portion is manufactured by the strong acid process. | The particular hazard cited is associated with the workplace, and is therefore under OSHA jurisdiction. EPA has no data to indicate that isopropyl oils are present in effluents, emissions, or wastes from production facilities where isopropyl alcohol is made by the strong acid process. | | |
| Isopropyl alcohol<br>67-63-0 | Domestic production: 750,610,500 lbs*<br><br>Imports: 32,623,500 lbs*<br><br>*some site limitations<br><br>38 producers and importers in 7 SFRs.<br><br>Public Record Only | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Melphalan<br>531-76-0 | Not reported for TSCA Inventory | Because malphalan is a pharmaceutical, it is of minimal regulatory interest to EPA. The Agency has no data to indicate its presence in effluents, emissions, or wastes from pharmaceutical manufacturers. | | |
| Mustard gas<br>505-60-2 | Not reported on TSCA Inventory | As a chemical warfare agent, mustard gas would be excluded from regulation under most laws by the national security clause contained in each. There is no indication of commercial scale manufacturer for any other purpose than would be subject to EPA regulations. | | |
| 2-Naphthylamine<br>91-59-8 | Domestic production: None reported<br><br>Imports: Not reported<br><br>One company reported for the TSCA Inventory, but did not indicate volume, nor if they were a manufacturer or importer.<br><br>Public Record Only | Since 2-naphthylamine may be manufactured at only one site EPA must assign this chemical a low regulatory priority. | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Nickel<br>7440-02-0 | Production aggregated for :<br>Nickel<br>Anhydrous nickel acetate<br>Nickel ammonium sulfate<br>Nickel carconate<br>Nickel carbonate hydroxide<br>Nickel carbonyl<br>Nickel chloride<br>Nickel flouride<br>Nickel oxide<br>Nickel subsulfide<br>Nickel sulfamate<br>Nickel sulfate<br>Nickel sulfide<br>Nickel trioxide<br>Nickelous hydroxide<br><br>Domestic production: 168,883,000 lbs<br><br>Imports: 424,748.00 lbs<br><br>137 producers and importers in 10 SFRs<br><br>Public Record Only | Effluent guidelines for certain industrial categories.<br><br>Water Quality Criteria<br><br>Assessments are in progress to determine if NESHAPs or other Clear Air Act regulations would be appropriate for nickel and/or any of its compounds. | Establishes control over nickel in certain effluent through permits issued under NPDES. Carcinogenicity is not a factor in developing effluent guidelines.<br><br>Proposed 7/79. Do not address carcinogenicity. Subject to revision in final. | 40 CFR 413, 415, (portions)<br><br>44 FR 144, p. 43660, et seq. |
| Nickel ammonium sulfate<br>15699-18-0 | Aggregated under nickel | Hazardous spill regulation designating harmful quantity, requiring reporting of spills, and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Nickel carbonyl 13463-39-3 | Aggregated under nickel | Nickel carbonyl is being assessed under Clean Air Act authorities, expecially because it has been cited as a possible contaminant of diesel fuel and present in-exhaust from diesel vehicles. To date, tests have been inconclusive. | | |
| Nickel chloride 7718-54-9 | Aggregated under nickel | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| Nickel hydroxide 12054-48-7 | Aggregated under nickel | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Nickel sulfate | Aggregated under nickel | Hazardous spill regulation designating harmful quantity, requiring reporting of spills and imposing penalties. | This regulation was promulgated in October 1979. Its goal is to encourage greater care in handling and shipment of chemicals. Does not address carcinogenicity. | 40 CFR 117 |
| N, N-Bis(2-chloroethyl) 2-naphthylamine 494-03-1 | Not reported for TSCA Inventory | IARC cites this substance as a pharmaceutical, but there is no indication that it is used in the United States for this or any other purpose. Thus, EPA is not concerned with regulating it. | | |
| Oxymetholone 434-07-1 | Not reported for TSCA Inventory | Because oxymetholone is a pharmaceutical, EPA has minimal regulatory interest in it. Because there is no evidence of domestic manufacture, it is unlikely that EPA will investigate sources for possible regulation. | | |
| | | | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Phenacetin<br>62-44-2 | Domestic production: 550,000 lbs<br><br>Imports: 55,000 lbs<br><br>7 producers and importers in 3 SFRs<br><br>Public Record Only<br><br>Uses:<br>Pharmaceutical (see FDA entry)<br>Stabilizer for hydrogen peroxide (indications that this is only in veterinary medical products) | Because phenacetin is a pharmaceutical, EPA has minimal regulatory interest in it. The Agency has no indication of its presence in effluents, emissions, or wastes from pharmaceutical manufacturers.<br><br>The fact that phenacetin was reported for the TSCA inventory indicates that there may be other uses which should be investigated for possible control. The relatively small production volume, compared with other chemicals (including carcinogens) of concern, may limit interest for the foreseeable future. | | |
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| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Phenytoin<br>57-41-0 | IARC review also discussed monosodium salt (CAS # 630-93-3). Phenytoin was not reported for the TSCA Inventory.<br><br>Phenytoin, monosodium salt<br><br>Domestic production: 500 lbs<br><br>Imports: None reported<br><br>3 producers and importers in 2 SFRs<br><br>Public Record Only | Because phenytoin and its monosodium salt are pharmaceuticals, EPA has minimal regulatory interest in them. The Agency has no indication of their presence in effluents emissions, or wastes from pharmaceutical manufacturers.<br><br>The fact that the monosodium salt of phenytoin was reported for the TSCA Inventory indicates that there may be other uses which should be investigated for possible control. The small production volume, compared with other chemicals (including carcinogens) of concern, may limit interest for the foreseeable future. | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Soots, tars, and oils<br>No CAS # | | | | |
| Coal tar<br>8007-45-2 | Domestic production: 34,847,000 lb (1975) | | | |
| Coal tar neutral oils, no CAS # | Domestic production: 2,019,000 lb (1975) | RPAR issued regarding pesticides containing coal tar, coal tar neutral oil and creosote | Rebuttal data are under review. The notice of proposed determination is scheduled for publication in 6/80. | 43 FR 202, p. 48154 et seq. |
| Creosote<br>8021-39-4 | Domestic production: 948,000,000 (1976)<br>Pesticide use reports (from OPP) | | | |
| Coke oven emissions<br>No CAS # | Unreported inadvertant by-products | Discussed in second report under PAH/BAP, as this is the presumed fraction of concern. | | |

| Substance (CAS #) | Production (Including) Imports & Exports) | Regulation | | |
|---|---|---|---|---|
| | | Regulations and Other Actions | Effects of Regulations and Other Actions | Citations |
| Vinyl chloride<br>75-01-4 | Domestic production: 6,900,000,000 lbs*<br><br>Imports: None reported<br><br>*Some site limitations<br><br>17 producers in 4 SFRS<br><br>Public Record Only<br><br>Population potentially exposed: 4,600,000 people live within five miles of the facilities subject to NESHAPs. | NESHAP's addressing vinyl chloride emissions from VCM production and polymerization, and certain ethylene dichloride manufacturing facilities<br><br>Water Quality Criteria<br><br>Cancellation/supervision of all VCM containing pesticides registered for use in homes, food handling establishments, hospitals, and enclosed areas. | Impose engineering controls that have been shown to reduce emissions by 95% over pre-control levels.<br><br>Proposed 3/79. Subject to revision in final<br><br>Most production for these uses had been ceased prior to this action. It permitted recall of existing stocks. | 40 CFR 61.60 -.17<br><br>44 FR 52, p. 15926 et seq.<br><br>40 FR 3934 |

FOOD AND DRUG ADMINISTRATION

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Aflatoxins | | None | None | Contaminant of corn, corn products, cottonseed, peanuts, animal tissue, milk, milk products, eggs | | Entire population | Oral | Very low 0.148-0.490 µg/day (est.) | Daily | | Years | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | Aflatoxins were found to be unavailable contaminants of food & tolerance levels of 15 ppb total aflatoxins in peanut products proposed in December 1974 and should be issued soon. Enforcement action levels of 20 ppb total aflatoxin in shelled peanuts & peanut products & 0.5 ppb aflatoxin $M_1$ in fluid milk products are in effect. | Holds human exposure to lowest practicable level. |
| Arsenic | | | | Naturally occurring especially in ocean fish and crustaceans | | Entire population, especially seafood eaters. | Oral | Low 0.02 mg/day | Daily | | Years | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | No specific action taken to decrease naturally occuring levels of arsenic | Not applicable |
| Arsenic | | | | Present in drugs used as animal feed additives and subsequently becomes a residue of meats consumed | | Entire population | Oral | Low | Daily | | Years | FDA-Bureau of Foods & Bureau of Veterinary Medicine | Food, Drug, and Cosmetic Act | Both organic and inorganic arsenics are regulated under CFR 21 §58.60 §88.530 §88.62 180.334 §88.120 180.335 None of the regulated arsenic compounds are those that have been associated with occupational cancer. No data on their carcinogenic properties have been developed. | Limits exposure from residues in meats obtained from treated animals. Seems quite effective for poultry less so for swine. In terms of residual arsenic in treated animals, there is no data to indicate that dietary arsenic is carcinogenic |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Asbestos | | | | May occur as a contaminant of food or beverage from contact with adhesives, repeat use polyester resin articles, phenolic resin molded articles, & repeat use rubber articles | | Entire population | Oral | Assumed very low or "virtually nil" | Daily | | Years | FDA-Bureau of Foods | Food, Drug and Cosmetic Act | Most permitted uses approved when asbestos was not known to be implicated as a carcinogen. At present there are no data available to estimate the levels of migration of asbestos into foods from the regulated uses. It is assumed that under good manufacturing practice, there will be "virtually nil" or "deminimus" migrationof asbestos into human foods. Regulations include 175.105 177.2Y10 177.2420 177.2600 | Original regulations assmed that migration to food would be "virtually nil" under the conditions of use. Further reductions would require new estimates of how much asbestos is actually getting into food and development of appropriately sensitive detection methods. |
| Asbestos | | | | Dental filling materials, particulary temporary cements | | Unknown (many dental patients) | Oral | Not known | Unknown | | Years | FDA-Bureau of Medical Devices | Food, Drug, and Cosmetic Act | No regulatory history and no regulations issued to date. | No regulations in effect. |
| Bis(Chloromethyl) ether | | | | Arise as possible metabolites of some dental restorative materials | | $10^5$/yr, Dental patients | Oral | Very low | Yearly or less assuming a peak metabolic accessability) | | Hours or less (decompose in water) | FDA-Bureau of Medical Devices | Food, Drug, and Cosmetic Act | No regulations promulgated by FDA-BMD | |
| Chloromethyl methyl ether | | | | | | $10^5$/yr, Dental patients | Oral | Very low | | | Hours of less (decompose in water) | FDA-Bureau of Medical Devices | Food, Drug, and Cosmetic Act | No regulations promulgated by FDA-BMD | |
| | | | | | | | | | | | | | | | |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Cadmium | | | | Naturally present in food and drinking water | | Entire population | Oral | Low 52µg/day (est.) | Daily | | Years | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | Cadmium is not regulated as a food or feed additive nor are there tolerances for its occurrences in food and water. No action has been taken on cadmium as a carcinogen because the data available are not adequate to access its carcinogenicity via dietary exposure. | Not applicable |
| Cadmium | | | | Dyes in dental cements and porcelains, tubing, lubricant, and stabilizer for polymers | | Not known | Oral | Not known presumed very low | Daily | | Years | FDA-Bureau of Medical Devices | Food, Drug, and Cosmetic Act | No regulatory action, need to clarify position on colors used in medical devices. No action has been taken on cadmium as a carcinogen because the data available are not adequate to access its carcinogenicity via dietary exposure | Not applicable |
| Carbon black (Soots, tars, and oils) | | | | As a pigment in food containers, molded articles, and rubber articles | | | Oral | Very low | Daily | | Years | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | 21 CFR 175.2 limit the migration of carbon black used in food packages and manufactured articles to "nil" and prohibits use of carbon blacks which contains PNAH. | Prohibits use of carbon black which would result in release of measurable PNAH. |
| Carbon black (Channel black) (Soots, tars, and oils) | | | | As a color additive for foods, drugs, and cosmetics. | | Entire population | Oral | | Daily | | Years | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | Commercially used prior to 1960 Provisional Listing 1960 Listing Terminated 1976 41FR41857(1976) 21 CFR81.10 (g) | Prohibits use of carbon blacks in foods, drugs, or cosmetics (Lack of Safety) (no adequate method to measure polynuclear aromatic hydrocarbons) |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistance | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Coal Tar (Soots, tars, and oils) | | | | To treat skin disorders | | | Topical | Medium .1-.01 gm/application | Bi-weekly (varies) | | Years | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | Most products are OTC; they are currently under review for safety, efficacy and labeling | Present labeling will be upgraded to limit suggested usage |
| Chloramphenicol | | | | Antibacterial, Anti-rickettsial Drug | | 120,000-150,000 patients/yr., 90% of whom are in hospitals when treatment given. | Oral | High 50-100 mg/kg day | 4 times per day orally | | | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | Regulated as a prescription drug. Systematic dosage forms bear physician directed labeling which warns of its oncogenic activity (leukemia) in humans. The topical preparations have no such warning. The label advises that unnecessary exposure be avoided. | To warn the physician against indiscriminant use of chloramphenicol because of its oncogenic activity. |
| | | | | | | | Topical | 0.5-1.0% formulation | 4-8 times per day | | | | | | |
| Chloramphenicol | | | | Illegal use in food producing animals Legal use in non-food producing animals. | | Unknown | Oral | Unknown | Unknown | | | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | Use restricted to non-food producing animals as an antibiotic. The Bureau of Foods is, however, aware of illegal use in food producing animals but has no adequate methodology to detect residues and no monitoring is done. | Lack of a residue monitoring capability prevents FDA from acquiring knowledge about the possible occurrence of residues in food. |
| Chromium | | | | Trace element naturally occuring in food and water. Used as an adhesive additive and pigment for rubber products | | Entire population | Oral | Low 53 µg/day (est.) | Daily | | Years | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | No specific regulations or tolerances for dietary exposure. Regulated under 21CFR175.105 for adhesives and 21CFR177.2600 for rubber products No action has been taken on chromium as a carcinogen because the data available are not adequate to assess its carcinogenicity via dietary exposure. | Not applicable for dietary sources. Regulated uses are based on an assumption that "all" migration of chromium will occur. |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Chromium | | | | Salts liberated from corrosion of alloys in implants, cranioplasty plates, and orthopedic implants. | | $10^4$ ear, nose, and throat patients<br>$10^5$ dental patients<br>$10^6$ cardio vascular patients<br>$10^4$ cranioplasty plates<br>$2 \times 10^5$ orthopedic implants | Implantation | Unknown (presumed very low) | Daily | | Years | FDA-Bureau of Medical Devices | Food, Drug, and Cosmetic Act | No regulations have been promulgated. Testing the carcinogenic potential of chromium salts liberated by corrosion of alloy has been suggested to NCI. | Not applicable |
| Cyclophosphamide | | | | Human drug for treatment of myeloproliferative disorders solid malignancies. Investigational use for immunosuppressive non-malignant diseases such as rheumatoid arthritis, chronic glomerulonephrosis, and nephrotic syndrome. | | 200,000-300,000 patients/year, one third hospital ordered one quarter administered in the physicians office and the rest administered by the patient via prescription | Oral, I.P. | High 1-5 mg/kg/day | Daily | | | FDA - Bureau of Drugs | Food, Drug, and Cosmetic Act | Prescription drug use for treatment of neoplasms. The package insert has clear warnings of the induction of secondary malignancies which may occur several years after treatment has discontinued. | Provides a mode of treatment that will prolong the life of cancer patients. The physician is provided with information required for a benefit vs. risk assessment on each patient<br><br>Use in non-malignant diseases is investigational but could allow exposure of very young children, young adults, and adults to doses which might induce future malignancies. More rigorous education of physicians in this danger may be advisable |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Diethylstilbestrol (DES) | | | | Prescribed for threatened abortion, menopause vasomotor symptoms, atrophic vaginitis, kraurosis vulvae, female castration, primary ovary failure, breast cancer, carcinoma of prostate, uterine bleeding, and post partum breast engorgement. | | Over 500,000/year with two-thirds of use in hospitals Most hospital use is for treatment of neoplastic disease on a continuous basis. Most neoplastic patients are male. | Oral I.V. | Medium 1-15 mg/day | Daily | | | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | In late 40's and early 50's DES was prescribed exclusively for threatened abortion. This use declined as epidemiologic studies demonstrated DES to not be effective in preventing abortion accidents. In 1971 further epidemiologic data proved a relationship between DES intrauterine exposure and clear cell adenocarcinoma of the vagina of female offspring. FDA has since required product labeling to state that DES is contraindicated for use in pregnancy. Dispensing an estrogen patient package insert with each new prescription became a regulation in 1977. Special estrogen labeling is required to be supplied to physicians which detail the risks involved with administering estrogens. | The use of DES in pregnant woman is listed as contra-indicated. Special patient package inserts and physician estrogen labeling information is required by regulation. The use of such education material will inform both the patient and the doctor to the risks associated with DES. |
| Diethystilbestrol (DES) | | | | Growth promotant for cattle and sheep which becomes a residue in edible meat. | | Entire population | Oral | Very low less than 10 ppb | Daily | | | FDA-Bureau of Foods Bureau of Veterinary Medicine | Food, Drug, and Cosmetic Act | Because DES has been shown to be a carcinogen in animals and has been associated with carcinogenesis in humans, a regulation was published in the Federal Register (FR 44:39367) on July 6, 1979 to revoke all uses of DES in food producing animals. On August 3, 1979, a stay of the effective date for revoking DES until November 3, 1979, was published in the Federal Register. There are presently two court actions before the Court of Appeals for the District of Columbia. | Completely remove the risk of continuous exposure to DES as a residue in meat and meat products. |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Hematite | | | | To color dental restoratives | | | Oral | Very low | | | Years | FDA Bureau of Drugs | Food, Drug, and Cosmetic Act | None | Not applicable |
| Melphalan | | | | Treatment of multiple myeloma and epithelial ovarian cancer | | 30,000-50,000/year | Oral I.V. | Medium 6 mg/day | 5 days per month | | | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | Approved drug for treatment of myeloma and epithelial ovarian cancer investigational use only for certain other cancers. | Use restricted to Bureau of Drugs approved treatments. |
| Methapyrolene | | | | Over the counter (OTC) use as a sedative-sleep aid, cough, cold, and appetite suppressant. | | Entire population is at potential risk. | Oral | High Maximum exposure exposure without abuse is 125 mg/day | Daily | | | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | Methapyrolene was approved for use in OTC preparations until June 1979. In 1979 animal data was presented which indicated methapyrolene is a strong carcinogen. Upon informing the drug industry, they agreed to initiate a Class II Level C recall as specified in 21CFR7.1. No human data has been received which shows methapyrolene is or is not a carcinogen in humans. | Brought about removal of all methapyrolene products from the consumer markets and ceased further marketing of any methapyrolene containing drugs. |
| | | | | | | | | | | | | | | | |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NCHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Nickel | | | | Naturally occurring trace element in food and water. Trace amounts may enter food from use of stainless steel cookware. Stainless steel implants and other alloys may expose patients. | | Entire population for naturally occur nickel in food. | Oral and | Low 300-600 µg/day from food and water. | Daily | | | FDA-Bureau of Foods Bureau of Medical Devices | Food, Drug, and Cosmetic Act | Not regulated as a food additive. No regulations on nickel present in implants. | Not applicable. |
| | | | | | | Stainless steel implants. $10^8$ cardiovascular patients $10^7$ nose and ear patients $10^5$ orthopedic patients | Implant | Implant exposure not known. | | | | | | No action has been taken on nickel as a carcinogen because the data available are not adequate to assess its carcinogenicity via dietary exposure. | |
| Oxymetholone | | | | Adjuvant therapy in senile and post menopausal osteoporosis; previous to 1972 used for treatment of anemia | | 50,000 to 100,000 patients/year | Oral | 1-5 mg per kg | Daily | | | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | Oxymetholone as indicated only for treatment of anemia caused by deficient red blood cell production, and was approved in 1972 for safety and effectiveness. Since 1972 all indications except "probably" effective as adjuvant therapy in senile and postmenopausal osteoporosis have been deleted from the labeling pending further investigation of this less than effective indication. | In 1972, FDA required a labeling revision in the adverse reaction section that would include a statement on the occurrence of hepatocellular neoplasms and pelliosis hepatis in association with anabolic androgenic therapy. |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Phenacitin | | | | Over the Counter (OTC) analgesic and antipyretic | | Potentially entire population | Oral | High 1 gram/day | Daily as needed | | | FDA_Bureau of Drugs | Food, Drug, and Cosmetic Act | Phenacitin has been reviewed by the Advisory Review Panel on OTC Internal Analgesic, antipyretic, and antirheumatic products & categorized as an effective OTC analgesic and antipyretic but not safe for OTC use. The FDA has initiated administrative proceedings to accomplish this but objections have been raised concerning the validity of the carcinogenesis data. The FDA is thus not in a position, at the present time, to call phenacitin a known human carcinogen. It can claim it as an animal carcinogen with some human data available but inadequate to permit human carcinogenicity evaluation. | The proposed action would remove phenacitin from over the counter (OTC) preparations. |
| Petrolatum and Mineral oil (oils) (Soots, tars and oils) | | | | Release agent in bakery & confection products and as a protective coating on fruits and vegetables | | Entire population | Oral | Medium 50 mg/day | Daily | | | FDA-Bureau of Foods | Food, Drug, and Cosmetic Act | Must meet specifications given in 21CFR171.678 and 21CFR171.880 | Limits the amount of Polynuclear Aromatic Hydrocarbons that may be present to "nil" |
| | | | | | | | | | | | | | | | |

# WORKSHEET FOR REPORTING INFORMATION ON ENVIRONMENTAL CARCINOGENS

| Chemical Identification | | Domestic Production (lbs/yr) | Imports (lbs/yr) | Usage | Number and Population Exposure | | Exposure Information | | | | | Regulatory Considerations | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name | CAS Number | | | | NOHS | Other Exposure Estimates | Route | Intensity | Frequency | Absorption | Environmental Persistence | Regulatory Agency | Regulatory Authority | Regulatory History and Regulatory | Effect of Regulation |
| Phenytoin | | | | Prescription drug for control of grand mal convulsive seizures, psychomotor seizures, & status epilepticus | | Not available at present time but can assume a major segment of the epileptic population would be exposed. | Oral and parenteral | High around 300 mg/day orally I.V. 200-350 mg/day | Daily | | | FDA-Bureau of Drugs | Food, Drug, and Cosmetic Act | Regulated as a prescription drug. The Bureau of Drugs points out that the scientific data are not conclusive to call phenytoin a "known human carcinogen." The problem has been sent to an Advisory Committee and their recommendation will be considered before any statement is issued from FDA. | No specific regulatory action will be taken until an advisory opinion has been submitted. |
| Vinyl chloride | | $2.4 \times 10^9$ kg (1973) | | Present as unreacted monomer (VCM) in PVC products | | | | | | | | FDA-Bureau of Drugs | | Any drug products containing VC must pass through the New Drug Application process 39 FR30830(1974) | Has eliminated the use of VC in drug products and as a propellant vehicle in aerosol products. |
| | | | | a. Medical Devices | | | I.V. | Very low | Yearly or less | | | Bureau of Medical Devices | | | |
| | | | | b. Food Containers | | | Oral | Very low (ppb) | Daily | | | Bureau of Foods | | Published notice to regulate VCM in packaging material, 40FR40528 (1975) but rules were not finalized. | This has alerted manufacturers to the need to monitor their packaging materials for VCM. BATF has banned use of PCV containers for alcoholic beverages based upon FDA work. |

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Aflatoxins | No estimates | (Food contaminant) | Ingestion | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| 4-Aminobiphenyl | 1,000 | Diphenylamine workers<br>Research workers | Inhalation<br>Percutaneous absorption | Lowest feasible level | Protective clothing, respirator and hygiene, facilities<br>medical surveillance program training requirements<br>exhaust fan requirements<br>open vessel operations prohibited<br>contamination control requirements<br>sign requirements for regulated areas; labelling requirements for containers | May 18, 1973 Emergency Temporary Standard<br>protective clothing and hygiene requirements for workers<br>open vessel operations restricted engineering requirements<br>February 11, 1974 Final standard current regulations effective (29CFR-1910.1011) |
| Arsenic | 545,000 | Arsenic workers<br>Brass makers<br>Bronze makers<br>Ceramic makers<br>Copper makers<br>Dye makers<br>Hide preservers<br>Herbicide and insecticide makers<br>Lead smelters<br>Paint makers<br>Printing ink workers<br>Silver refiners | Inhalation of dusts and fumes<br>Ingestion of dusts and fumes | 0.5 mg/m$^3$ 8 hr TWA as As (organic)$_3$<br>10 µg/m$^3$ 8hr TWA (inorganic)<br>No skin or eye contact with As Cl$_3$<br>monitoring requirements | Protective clothing, respirator and hygiene facilities<br>medical surveillance program<br>training requirements<br>housekeeping requirements<br>sign requirements for regulated areas; labelling requirements for containers | 1962 Walsh-Healy 0.5 mg/m$^3$ maximum allowable concentration<br>August 27, 1971 OSHA takeover standard 0.5 mg/m$^3$ 8 hr TWA As (arsenic and compounds) 1 mg/m$^3$ 8 hr TWA (calcium arsenate) 0.15 mg/m$^3$ 8 hr TWA (lead arsenate)<br>June 30, 1978 Final standard current limit effective (29CFR1910.1018) |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Asbestos | 2,466,000 | Asbestos miners<br>Auto mechanics<br>Brake lining workers<br>Carpenters<br>Electricians<br>Insulation workers<br>Laggers<br>Masons<br>Painters<br>Refitters<br>Shingle makers<br>Shipwrights<br>Steamfitters<br>Textile workers<br>Vinyl asbestos tile workers | Inhalation<br>Ingestion | 2 fibers/cc > 5 um in length 8 hr TWA<br>10 fibers/cc > 5 um in length ceiling<br><br>monitoring requirements | Medical surveillance program<br>Housekeeping and waste disposal requirements<br>Protective clothing, respirator and change room requirements in areas where engineering and work practice controls are not sufficient to lower asbestos to permissible levels<br>sign requirements for regulated areas | 1951 Walsh-Healy<br>5 mppcf maximum allowable concentration<br><br>1969 Walsh-Healy<br>12 fibers/cc > 5 um in length or 2mppcf 8 hr TWA<br><br>August 27, 1971<br>OSHA Takeover Standard Tremolite 20 mppcf or 20 mg/m$^3$ 8 hr TWA %$SiO_2$<br><br>Asbestos 12 fibers/cc 5 um in length or 2 mppcf 8 hr TWA<br>December 7, 1971<br>Emergency Temporary Standard<br>5 fibers/cc > 5 um in length 8 hr TWA<br>10 fibers/cc > 5 um in length ceiling permissible for up to 15 min/hr., 5 hr/day<br><br>January 11, 1972<br>Standard coverage expanded to include ship repairing, shipbuilding shipbreaking, and longshore workers<br><br>July 7, 1972 Final standard<br>5 fibers/cc > 5 um in length 8 hr TWA<br>10 fibers/cc > 5 um in length ceiling |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Asbestos (continued) | | | | | | July 1, 1976 current limit effective (29CFR1910.1001) |
| Auramine | 3,000 | | Not available | Regulated by the general duty clause+ | | (PL 92-596 1970) |
| Benzene | 2,976,000 | Adhesive makers<br>Asbestos products impregnators<br>Benzene hexachloride makers<br>Burnishers<br>Carbolic acid makers<br>Chemists<br>Chlorinated benzene workers<br>Detergent makers<br>Dry battery makers<br>Dye makers<br>Furniture finishers<br>Glue makers<br>Linoleum makers<br>Maleic acid makers<br>Nitrobenzene makers<br>Petrochemical workers<br>Putty makers<br>Rubber makers<br>Styrene makers<br>Welders | Inhalation<br>Percutaneous absorption | 1 ppm 8 hr TWA<br>6 ppm 15 min TWA ceiling<br>No skin or eye contact with benzene liquid<br><br>monitoring requirements<br><br>(regulations stayed by order of the 5th District Court; appeal with U. S. Supreme Court pending) | Protective clothing and respirator requirements<br>medical surveillance program<br>training requirements<br>sign requirements for regulated areas, labelling requirements for containers | August 27, 1971 OSHA Takeover standard 10 ppm 8 hr TWA<br>May 21, 1977 Emergency Temporary Standard 1 ppm 8 hr TWA 5 ppm 15 min TWA ceiling<br>February 10, 1978 current standard promulgated (29CFR1010.1028) |
| Benzidine | 86,000 | Biochemists<br>Dye workers<br>Medical laboratory workers<br>Organic chemical synthesizers<br>Plastics workers<br>Rubber workers | Inhalation<br>Percutaneous absorption<br>Ingestion of dust | Lowest feasible level | Protective clothing, respirator and hygiene facilities<br>medical surveillance program<br>training requirements<br>exhaust fan requirements<br>open vessel operations prohibited | May 18, 1973 Emergency Temporary Standard protective clothing and hygiene requirements for workers |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Benzidine (continued) | | Wood chemists | | | contamination control requirements<br>sign labelling requirements for regulated areas; labelling requirements for containers | open vessel operations restricted<br>engineering requirement<br>February 11, 1974<br>Final Standard<br>current regulations effective (29CFR1910.1010) |
| Bis (chloromethyl) ether | No estimates | Ion exchange resin makers<br>Laboratory workers<br>Organic chemical synthesizers<br>Polymer makers | Inhalation<br>Possible percutaneous absorption | Lowest feasible level | Protective clothing, respirator and hygiene facilities<br>medical surveillance program<br>training requirements<br>exhaust fan requirements<br>open vessel operations prohibited<br>contamination control requirements<br>sign requirements for regulated areas; labelling requirements for containers | May 18, 1973<br>Emergency Temporary Standard<br>Protective clothing and hygiene requirements for workers<br>open vessel operations restricted<br>engineering requirements<br>February 11, 1974<br>Final standard<br>current regulations effective (29CFR1910.1008) |
| Cadmium | 359,000 | Alloy makers<br>Battery makers<br>Dental amalgam makers<br>Engravers<br>Metalizers<br>Printmakers<br>Pesticide workers<br>Solder workers<br>Textile printers<br>Welders<br>Zinc refiners | Inhalation of fumes or dust<br>Ingestion of fumes or dust | 0.1 mg/m$^3$ 8 hr TWA (fumes)<br>0.3 mg/m$^3$ ceiling (fumes)<br>0.2 mg/m$^3$ 8 hr TWA (dust)<br>0.6 mg/m$^3$ ceiling (dust) | | 1951 Walsh-Healy<br>0.1 mg/m$^3$ maximum allowable concentration<br>August 27, 1971<br>OSHA Takeover Standard<br>current limit effective (29CFR1910.1000) |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Chloramphenicol | 4,000 | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Chloromethyl methyl ether | No estimates | Organic chemicals synthesizers | Inhalation<br>possible percutaneous absorption | Lowest feasible level | Protective clothing, respirator and hygiene facilities<br>medical surveillance program<br>training requirements<br>exhaust fan requirements<br>open vessel operations prohibited<br>contamination control requirements<br>sign requirements for regulated areas; labelling requirements for containers | May 18, 1973<br>Emergency Temporary Standard<br>protective clothing and hygiene requirements for workers<br>open vessel operations restricted<br>engineering requirements<br>February 11, 1974<br>Final standard<br>current regulations effective (29CFR1910.1006) |
| Chromium | 4,412,000 | Anodizers<br>Copper etchers<br>Electroplaters<br>Glass workers<br>Lithographers<br>Metal workers<br>Oil purifiers<br>Photographers<br>Photogravers<br>Process engravers<br>Stainless steel workers<br>Textile workers<br>Welders | Percutaneous absorption<br>Inhalation<br>Ingestion | 0.1 mg/m$^3$ ceiling (chromic acid and chromates)<br>0.5 mg/m$^3$ 8 hr TWA (sol chromic$_5$ous salts)<br>1 mg/m$^3$ 8 hr TWA (metal and insol salts) | | 1952 Walsh-Healy<br>0.1 mg/m$^3$ maximum allowable concentration (chromic acid and chromates)<br>August 27, 1971<br>OSHA Takeover Standard<br>current limit effective (29CFR1910.1000) |
| Cyclophosphamide | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Diethylstilbestrol | 4,000 | | Not available | Regulated by the general duty clause+ | | (PL 92-596 1970) |
| Hematite | | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Isopropyl oils (IPD) | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Melphalan | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Mustard gas | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| 2-Naphthylamine | 1,000 | 2-Naphthylamine workers<br>Research workers | Inhalation<br>percutaneous absorption | Lowest feasible level | Protective clothing, respirator and hygiene facilities<br>medical surveillance program<br>training requirements<br>exhaust fan requirements<br>open vessel operations prohibited<br>contamination control requirements<br>sign requirements for regulated areas<br>labelling requirements for containers | May 18, 1973<br>Emergency Temporary standard<br>protective clothing and hygiene requirements for workers<br>open vessel operations restricted<br>engineering requirements<br>February 11, 1974<br>Final standard<br>current regulations effective (29CFR1910.1009) |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Nickel and Compound | 709,000 | Battery makers<br>Ceramic makers<br>Chemists<br>Dyers<br>Enamelers<br>Ink makers<br>Magnet makers<br>Oil hydrogenators<br>Paint maker<br>Pen point makers<br>Spark plug makers<br>Textile dyers<br>Varnish makers | Inhalation of dust or fumes | 0.001 ppm, 0.007 $mg/m^3$ 8 hr TWA (nickel carbonyl)<br>1 $mg/m^3$ 8 hr TWA (as Ni; metal soluble compounds) | | 1952 Walsh-Healy 1 ppm (nickel carbonyl) maximum allowable concentration<br>August 27, 1971 OSHA Takeover Standard current limit effective (29CFR1910.1000) |
| N,N-Bis(a-chloroethyl) 2 naphthylamine | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Oxymetholone | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Phenacetin | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| Phenytoin | No estimates | | Not available | Regulated by the general duty clause+ | | (PL 91-596 1970) |
| | | | | | | |

| Chemical | Number of Workers Exposed (A) | Types of Workers Exposed | Route of Exposure | OSHA Regulations | | Regulatory History |
|---|---|---|---|---|---|---|
| | | | | Exposure Limit | Additional Regulation (B) | |
| Soot, tars, oils | 121,000 (tars) | | Not available | 0.2 mg/m$^3$ 8 hr TWA (coal tar pitch volatiles) | | August 27, 1971<br>OSHA Takeover Standard<br>current limit effective<br>(29CFR1910.1000) |
| Vinyl Chloride | 3,547,000 | Polyvinyl resin makers<br>Organic chemical synthesizers<br>Rubber makers | Inhalation | 1 ppm 8 hr TWA<br>5 ppm/15 min TWA ceiling<br>No direct contact with liquid<br><br>monitoring requirements | Protective clothing and respirator requirements<br>medical surveillance program<br>training requirements<br>sign requirements for regulated areas;<br>labelling requirements for containers | 1952 Walsh-Healy<br>500 ppm maximum allowable<br><br>August 27, 1971<br>OSHA Takeover Standard<br>500 ppm, 1300 mg/m$^3$ ceiling<br><br>April 5, 1974<br>Emergency Temporary Standard<br>50 ppm ceiling<br><br>April 1, 1975<br>Final standard<br>current limit effective<br>(29CFR1910.1017) |

KEY:

(A) Based on NIOSH NOHS 1972-74 survey. An individual worker may be counted as being exposed to more than one substance.

(B) See Part 1910, Title 29 of the Code of Federal Regulation for specifics of requirements.

+ Public Law 91-596, Section 5(a)(1) states that each employer shall furnish "a place of empolyment free from recognized hazards that are causing or likely to cuase death or serious physical harm to his employee."

* From Occupational Exposure to Coke Oven Emissions, U.S. Department of Health, Education, and Welfare, NIOSH, 1973.



* U.S. GOVERNMENT PRINTING OFFICE : 1980 620-231/5139

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